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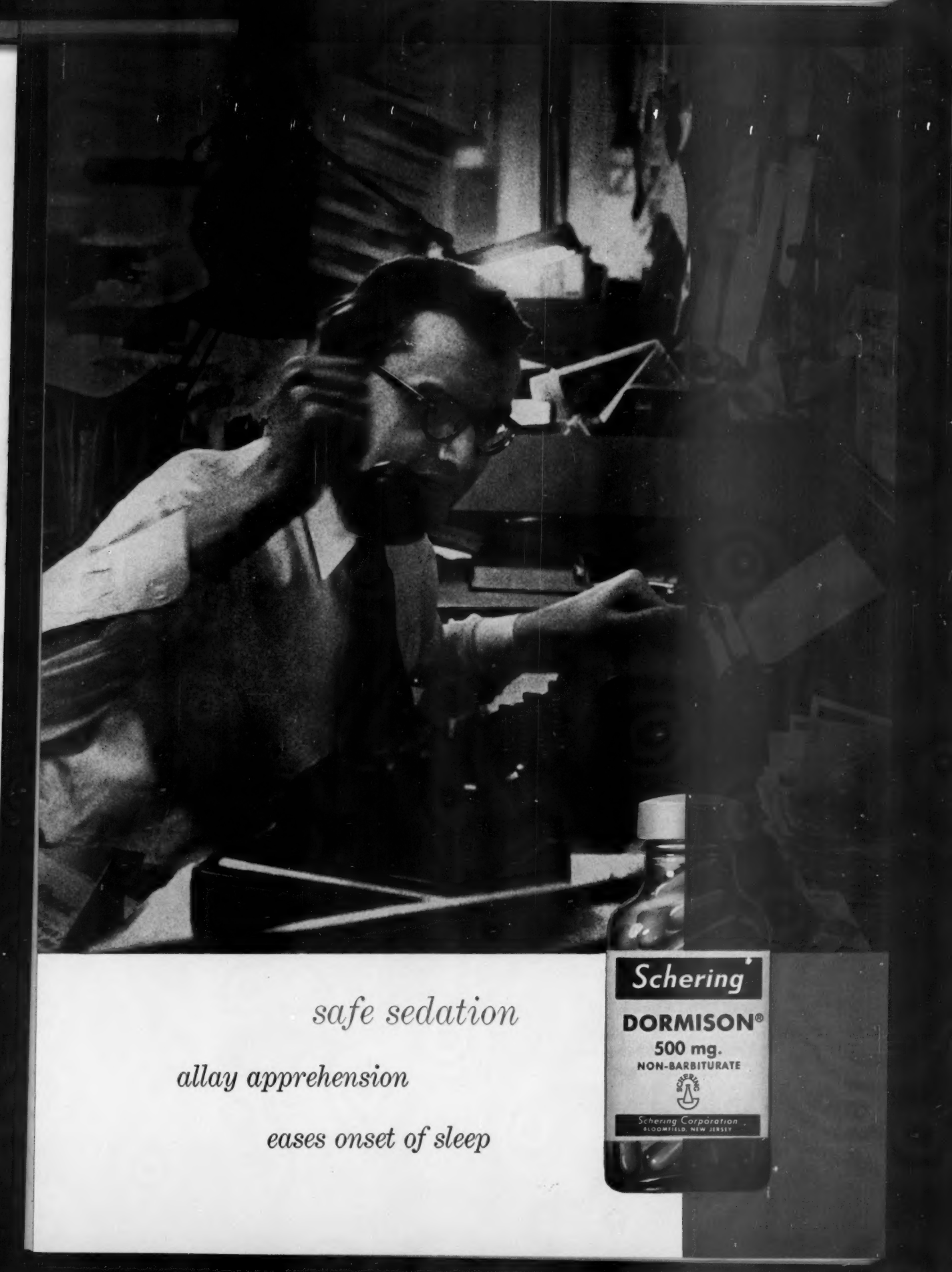

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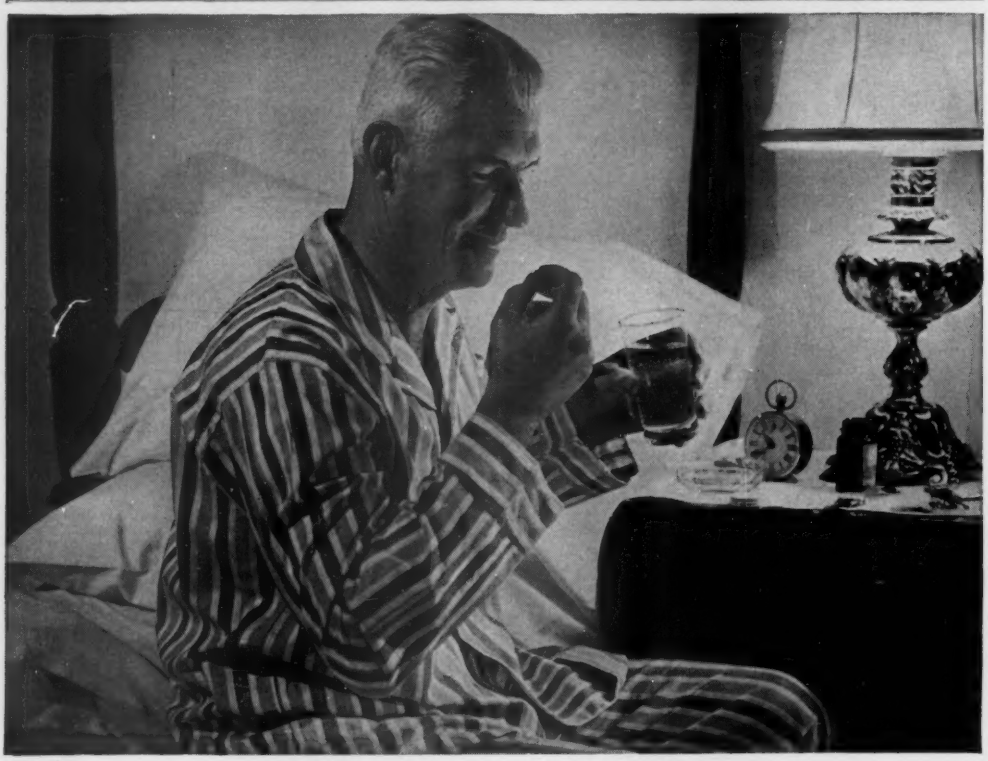

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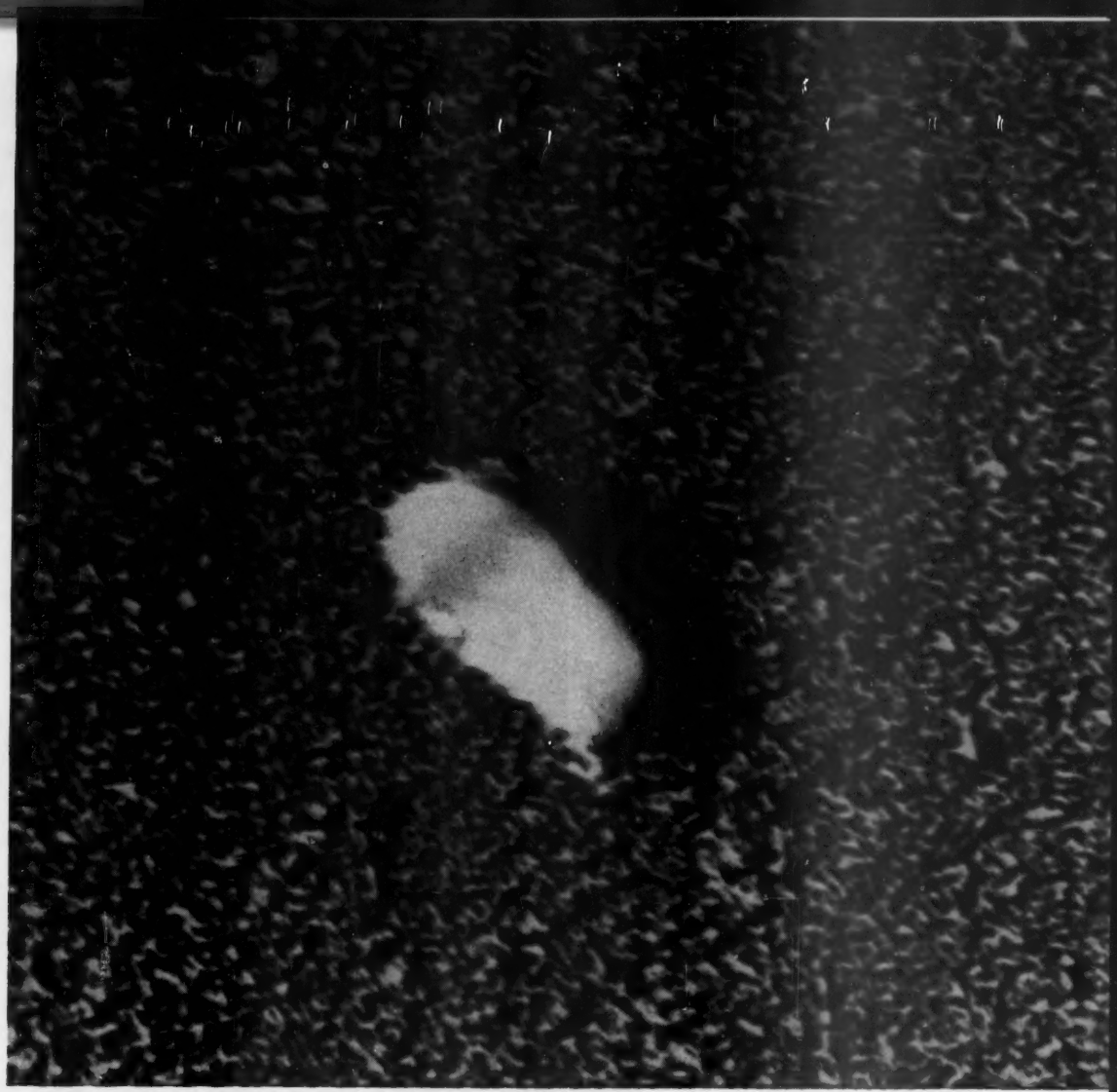

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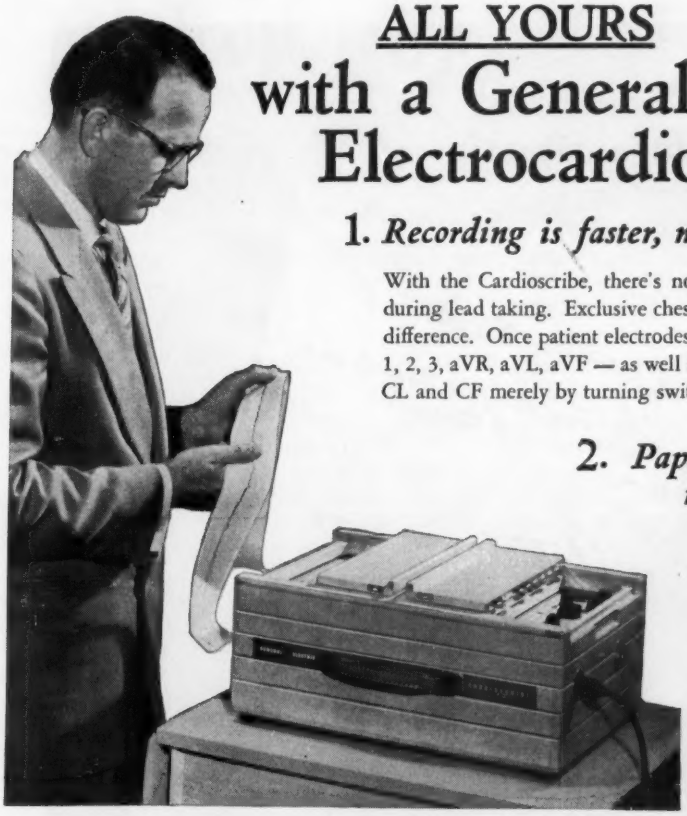

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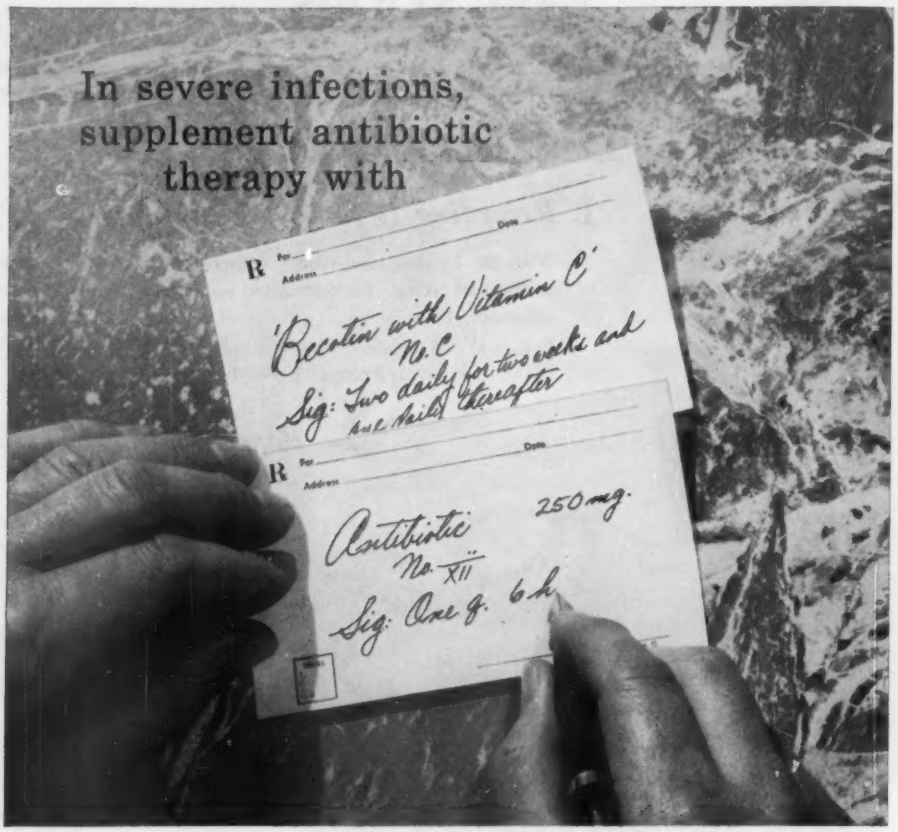

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Volume 252 FEBRUARY 17, 1955 Number 7

CARCINOMA AND THYROID NODULES

The Problem in an Endemic Goiter Area

J. MARTIN MILLER, M.D.*

DETROIT, MICHIGAN

MOST of the numerous articles on nodular goiter and thyroid cancer are written by surgeons and presumably for surgeons[1-7]; the papers of Crile[8-10] are a notable exception. Internists and general practitioners see most of the nodular goiters, and the majority of patients are never referred to the surgeon. The suspicious thyroid glands, however, are submitted for surgical scrutiny, as are the glands that are easily identifiable as cancer on physical examination. These not undesirable circumstances contribute measurably to the unintentional distortions in some surgical statistics. Time has produced little unanimity of opinion between the two groups. The figures of 20 and 25 per cent for cancer in nodular goiter have largely been recognized as not representative of the experience of most physicians. In 1954, however, Ravdin[11] cited a prevalence of 5 to 10 per cent and stated that most authors agree that all thyroid nodules should be removed. On the other hand, Sokal[12] regarded a figure of 0.2 per cent as representing the same condition.

As in most clinical problems, the ideal study material is not at hand and may never be. A planned investigation begun now may be worthless in twenty years because of such factors as the diminishing prevalence of nodular goiter in the Great Lakes area. Information such as that submitted by Hazard and Kaufman[13] from autopsy material has the possible disadvantage of being not representative of the living population and of lacking correlation with the clinical findings in any given case. As mentioned above, data garnered from surgical material are the result of a process involving a considerable selection. In general, the higher the referral practice of an institution reporting the statistics, the less likely the statistics to be representative of what the average reader and internist see. Another paper on the subject is justifiable only if new statistical and clinical information is submitted, and these data should preferably come from another source.

The clinical material at the Henry Ford Hospital presents a unique opportunity to study the types and prevalence of disease in a relatively unselected population. As such, it represents the practice seen by the average internist or a smaller clinical group. Patients come from a large metropolitan area and the many smaller adjacent communities. In contrast with the other large specialty centers, this hospital carries on a much larger nonphysician referral practice. During the ten-year period from 1943 to 1952 selected for study, there were 3,000,000 nonpediatric and nonobstetric outpatient and inpatient visits. From the hospital records of this large number of patients and from the examination of patients currently being seen for a variety of complaints and illnesses, the following facts were determined: the prevalence of clinical nodular goiter in the patient population; the frequency of cancer of the thyroid gland as an unsuspected finding in goiter surgery; and the rate of the biopsy diagnosis of thyroid cancer and its importance as a cause of death.

NODULAR GOITER

Three hundred women, twenty years of age or older, were examined in the diagnostic clinic of the hospital, and 300 inpatients were similarly examined. All observations were made by one observer, the positive findings being checked by independent examiners. Emphasis was placed on the nodules of at least 2 cm. because they offered little opportunity for dispute and because the general surgeon was usually willing to remove nodules of this size. It is, of course, realized that many thyroid cancers are 1 cm. or less in size at the time of metastasis. Women only were examined because nodular goiter among men in the present clinic population is so rare that a prohibitive number would have had to be examined before yielding representative figures. This form of selection does not allow determination of the true frequency of nodular goiter in the general population but permits a study of its relation to carcinoma. All patients were excluded who presented complaints related to the thyroid gland or a history of previous thyroid surgery. The results are given in Table 1.

A patient was considered to be from the endemic

*Associate physician, Division of Endocrinology, Henry Ford Hospital.

goiter area if she had lived at least twenty years in Michigan or adjacent goiter areas and had spent at least half her first twenty years in the same area. The difference between hospitalized and clinic patients was not significant. Twenty-eight patients, or 4.6 per cent of the 600 studied, had nodules of 2 to 5 cm., 40, or 6.6 per cent, nodules 1 or 2 cm., 7, or 1.1 per cent, nodules of 2 cm. or larger that seemed to be solitary, and 8, or 1.3 per cent, "single" nodules that were 1 or 2 cm. in size. The number of nodular thyroid glands was not large enough to give a true picture of the frequency in endemic versus nonendemic areas, but the glands of the patients from endemic areas represented 67 per cent of the total and contained 71 per cent of the nodules. This is certainly not a striking difference. Thus, the prevalence of 2-cm. nodules in these female patients is 4.5 per cent. To estimate the frequency in male patients, the sex ratio of 6:1 in patients treated surgically for nodular goiter is used. This gives a probable figure of 0.7 per cent in men. Since women represent 60 per cent of the total patients seen, the over-all figure would be 3 per cent. In 300,000 nonobstetric and nonpediatric new-patient registrations during the ten-year period there would have been 9000 nodular goiters in which the largest nodule was at least 2 cm.

Table 1. *Prevalence of Thyroid Nodules in Unselected Patients.*

Classification	No. of Patients	Patients from Endemic Area	Average Age	Patients with Nodules 2-5 Cm. in Size		Patients with Nodules 1-2 Cm. in Size	
				Number	Percentage	Number	Percentage
			yr.				
Outpatients	300	213	41	15	5.0	22	7.3
Inpatients	300	195	49	13	4.3	18	6.0
Totals	600	408		28		40	
Averages			45		4.6		6.6

Table 2. *Frequency of Thyroid Cancer in Relation to the Degree of Nodularity.*

No. of Nodules	Clinical Impression of Nodularity	Multinodular Goiter*	Pathological Diagnosis of Carcinoma
	No. of cases	No. of cases	No. of cases
Single	224	99	9 (4.0%)
Multiple	194	194	7 (3.6%)
Colloid	17	17	0 –
Totals	435	310	16 (3.7%)

*At least 2 nodules of 1 cm. or over in pathological specimen.

Unsuspected Thyroid Cancer

During the ten-year period of observation 435 thyroidectomies were performed for nontoxic nodular goiter. The operations for toxic nodular goiter were omitted from the statistics to facilitate comparison with other series and because the toxicity of the gland was often the factor that led the patient to the physician and to the operating room. This point is discussed below. All patients were excluded who had a definite clinical preoperative diagnosis of thyroid cancer or who presented themselves with metastatic disease. A suspicion of cancer on statistical grounds was not classified as a diagnosis. The ratio of women to men in this series was 6:1. With the same criteria used in the series not operated on, the ratio of patients from an endemic region to those from a nonendemic region was 2.5:1.0. The average age of the patient operated on was forty-five.

A clinical determination of the degree of nodularity is recorded in Table 2. These results bear out the observations of other authors on the inaccuracy of this judgment. Among all the glands described by the pathologist as containing a nodule of at least 1 cm., there were 16 cases of cancer, or 3.7 per cent of the total number of patients operated on. Table 2 also demonstrates that the percentage of unsuspected cancer in thyroid glands with nodules thought clinically to be solitary is not significantly different from that in glands with nodules considered to be multiple. It should be pointed out, however, that in 3 of the 7 glands diagnosed clinically as multiple, only 2 nodules were described, and in another 2, the enlargement was unilateral. A figure of 5.7 per cent represents the prevalence of carcinoma in the pathologically diagnosed solitary nodule. This has no practical application. There was 1 unsuspected cancer in about 250 cases of toxic nodular goiter.

Table 3. *Comparison of Mortality in Thyroid Cancer with That of More Common Types (1943-1952).*

Site of Cancer	No. of Pathological Diagnoses	No. of Deaths from Disease	Ratio of Diagnoses to Deaths
Thyroid gland			
"Papillary"	18	2	9:1
"Nonpapillary"	14	6	2.3:1
Totals	32	8	4:1
Stomach	308	237	1.3:1
Breast	448	224	2:1
Cervix	246	143	2:1
Rectum	349	170	2:1

New Cancers of the Thyroid Gland

A total of 32 new cases of histologically proved cancer were seen for the first time during the ten-year period. Follow-up observations on cases of this type were 100 per cent. These 32 patients represent 0.7 per cent of the total cases of cancer seen at the hospital. For contrast the figure for four other more common types of cancer is presented in Table 3. The data on all 32 cases are given in Table 4.

Table 4. *Complete Data on 32 Cases of Thyroid Cancer.*

Age	Sex	Preoperative Diagnosis	Pathological Diagnosis	Year of Operation	Follow-up Report (1953)
yr.					
50	M	Nodular goiter	Papillary adenocarcinoma	1952	No local or metastatic disease
34	F	Nodular goiter	Papillary adenocarcinoma	1952	No local or metastatic disease
32	F	Nodular goiter	Papillary adenocarcinoma	1952	No local or metastatic disease
40	F	Nodular goiter	Papillary adenocarcinoma	1950	No local or metastatic disease
51	F	Nodular goiter	Fetal adenoma with carcinoma	1944	No local or metastatic disease
46	F	Nodular goiter	Reticulum-cell sarcoma	1949	No local or metastatic disease
59	F	Nodular goiter	Adenocarcinoma	1952	No local or metastatic disease
54	F	Nodular goiter	Papillary adenocarcinoma	1951	No local or metastatic disease
23	M	Nodular goiter	Follicular adenocarcinoma	1951	No local or metastatic disease
42	M	Nodular goiter	Papillary adenocarcinoma	1949	No local or metastatic disease
58	F	Nodular goiter	Papillary adenocarcinoma	1951	No local or metastatic disease
62	F	Nodular goiter	Papillary adenocarcinoma	1948	No local or metastatic disease
43	F	Nodular goiter	Papillary adenocarcinoma	1944	No local or metastatic disease
40	F	Nodular goiter	Adenocarcinoma	1944	No local or metastatic disease
59	M	Nodular goiter	Fetal adenoma, with carcinoma	1945	No local or metastatic disease; reoperation for local recurrence, 1951.
40	M	Nodular goiter	Fetal adenoma, with carcinoma	1949	Local recurrence, 1953, with incomplete removal
40	F	Toxic nodular goiter	Adenocarcinoma	1948	No local or metastatic disease
21	F	Cervical adenopathy	Papillary adenocarcinoma	1945	No local or metastatic disease; reoperation for local recurrence, 1950.
23	F	Cervical adenopathy	Papillary adenocarcinoma	1951	No local or metastatic disease; reoperation for local recurrence, 1953.
51	M	Cervical adenopathy	Follicular adenocarcinoma	1952	Death, 1952, of unrelated carcinoma
36	M	Cervical adenopathy	Papillary adenocarcinoma	1949	No local or metastatic disease
15	F	Cervical adenopathy	Papillary adenocarcinoma	1950	No local or metastatic disease
27	M	Cervical adenopathy	Papillary adenocarcinoma	1947	No local or metastatic disease
28	F	Cervical adenopathy	Papillary adenocarcinoma	1947	No local or metastatic disease
50	F	Cervical adenopathy	Papillary adenocarcinoma	1951	No local or metastatic disease
56	M	Thyroid carcinoma	Adenocarcinoma	1952	Death after 2 mo.
53	F	Thyroid carcinoma	Adenocarcinoma	1947	Death after 4 days
63	M	Thyroid carcinoma	Papillary adenocarcinoma	1947	Death from complications of repeated surgery, after 8 mo.
61	F	Metastatic thyroid carcinoma	Papillary adenocarcinoma	1949	Death after 1½ yr.
61	M	Thyroid carcinoma	Adenocarcinoma	1945	Death after 3 mo.
22	F	Metastatic thyroid carcinoma	Adenocarcinoma	1943	Death after 6 mo.
53	F	Metastatic carcinoma	Adenocarcinoma	1949	Death after 2½ yr.

The carcinoma was an unsuspected finding in 17 patients. Sixteen lesions occurred in nontoxic cases, and 1 in a hyperfunctioning gland. In 1953 all patients were living, and only 1 had evidence of recurrent carcinoma. This patient and 1 other had an operation for local recurrence of the disease. Nine of the 16 patients had papillary adenocarcinomas, 1 a follicular adenocarcinoma, 3 fetal adenomas with carcinoma, 3 adenocarcinomas, and 1 a reticulum-cell sarcoma.

Eight patients were operated on because of lymph-node metastases, of which 7 were papillary adenocarcinomas and 1 a follicular adenocarcinoma. Two of these patients were reoperated on for local recurrence, and 1 patient died of an unrelated carcinoma. Seven patients were living and well without evidence of any metastases in 1953.

A preoperative diagnosis of carcinoma of the thyroid gland was made in 7 cases. In 2 the diagnosis had been made elsewhere, and 1 of these patients had survived for eight years with only radiation treatment. Two patients had a history of pre-existing

goiter — 1 for seven, and the other for twenty-five years. There were 2 pathological diagnoses of papillary adenocarcinoma and 5 of adenocarcinoma. Survival varied from a few days to two years — the average being ten months. In addition to these 7 deaths 1 patient with solid adenocarcinoma of the thyroid gland diagnosed ten years earlier was known to have died with the disease during the period of study. This was the only death among all the cases diagnosed in the previous twenty-five years and brings the total known deaths from carcinoma of the thyroid gland to 8 for the years 1943 to 1952.

Discussion

This study was prompted by the inapplicability of the thyroid-cancer statistics of Cole, Majarakis and Slaughter,[4] Cope et al.,[3] Ward,[14] Ravdin[11] and Cerise, Randall and Ochsner[6] to the practice of a Detroit internist. The rebuttal to the surgical point of view was admirably presented by Rogers, Asper and Williams in 1947,[15] Crile and Dempsey in 1948[9] and Sokal in 1954.[12,16] The objectionable feature of many surgical statistics — the inclusion of obvious thyroid cancer — has been eliminated in the series of Beahrs, Pemberton and Black[5] and Beal, Scholnick and Stevens.[17] The resulting figure for unsuspected cancer was reduced to 3.5 to 4 per cent in both, which is almost identical, perhaps fortuitously, with the frequency of 3.7 per cent in the present study. That this figure represents a still greater selection is attested by the fact that a maximum of 1 patient in 10 with nodular goiter was operated on. The majority of the patients — at least during the first eight years — underwent operation for some other reason than cancer eradication or prophylaxis. Almost half the patients who had thyroidectomies had glands of sufficient size or symptoms of such a type or severity that they were first seen in the general-surgery clinic and admitted to the hospital directly for a preoperative work-up. If the figures for estimated nodular glands seen and unsuspected carcinomas found are combined a prevalence of 0.2 per cent is derived. This corresponds to that found by Sokal[12] in his statistical analysis of data drawn from all parts of the country. This figure would be lower if the patients with nodular toxic goiters were included as well as those with nodules under 2 cm. in size. Surgical statistics are in error because they assume that the percentage of cancer in the patients whose thyroid glands were not operated on is the same as that in the patients undergoing thyroidectomy. The type of calculation used here is in error in the opposite direction because it assumes that all the nodular goiters not operated on were benign. If the assumption is made that thyroid cancer requiring operation would eventually become manifest, this number of clinically significant thyroid cancers not operated on must be very small as evidenced by the total of thyroid cancer seen. The actual prevalence of histologic cancer of the thyroid in nodular goiter cannot be calculated from this type of study. The figure of 0.2 per cent would approximate that of preclinical unsuspected cancer. If all the thyroid cancer seen was considered as arising in a nodular goiter, this figure would be only 0.4 per cent.

The surgical mandate for removal of nodular thyroid glands is based on three premises, which are considered in order: cancer of the thyroid gland is a disease of fatal termination; a cancer found unexpectedly has a much greater chance of cure than one that is clinically obvious; and removal of a nodular goiter eliminates a potential cancer.

Many authors have been alert to point out that the mortality of carcinoma of the thyroid gland based on autopsy statistics is not helpful. To obviate such just criticism, I have counted all deaths of patients from thyroid cancer occurring during a ten-year period, regardless of the year of diagnosis or the place of death. This number is 8 patients, or less than 1 a year. (In 1951 and 1952 alone, 7 cases of thyroid cancer were discovered at operation.) The significance of this number of deaths is made more apparent if it is related to the frequency of deaths from other types of cancer during the same period (Table 3).

These figures demonstrate that cancer of the thyroid gland as an entity is half to a third as malignant as the more common type of cancers listed, and the papillary variety is a fourth to a seventh as malignant. Of the 2 patients with papillary carcinoma who did die, 1 had been regarded as inoperable elsewhere and had survived eight years with only radiation therapy, and the other died of complications of repeat surgery. In the entire thirty-seven-year history of the Henry Ford Hospital and clinic, only 3 patients are known to have died with papillary carcinoma of the thyroid gland. In a series from Memorial Hospital in New York,[18] consisting of 38 per cent repeat operations on this type of cancer, 20 per cent of patients were dead after five years. Pemberton[19] reports a ten-year cure of 79 per cent, and deaths after this time are few, as noted by McDermott et al.[20] In Crile's[8] series of 24 cases of papillary cancer in which he did the initial operation, there were no deaths in five years. The recurrences in the series at the Henry Ford Hospital were usually the result of inadequate first operations. It seems that the over-all malignancy of thyroid cancer is of little value in estimating the results of prophylactic surgery since over half the tumors removed are of low malignancy.

Ward[14] emphasizes the high curability rate of thyroid cancer diagnosed at operation as compared with that diagnosed clinically. This is supposedly analogous to the malignant gastric ulcer or carcinoma in situ in the cervix. This point of view has been adequately refuted by Crile[10] and Rogers, Asper and Williams,[15] who maintain that the cancer found unexpectedly is most likely to be by nature a slow-growing neoplasm. The very malignant thyroid can-

cers can be cured by prophylactic total thyroidectomy in 20 per cent or less of the cases, for only in this number is a previous history of goiter obtained. The less malignant ones can be cured in a high percentage of cases when they become clinically manifest. In the present series the results in patients who presented themselves with lymph-node metastases tended to substantiate this. The follow-up period is admittedly quite inadequate, but the figures are suggestive.

The question of the importance of pre-existing goiter in the development of thyroid cancer cannot be settled by this study and perhaps may never be. Two of the 7 patients who died from the disease gave such a history. The evidence that papillary carcinomas are malignant from the beginning is impressive.[21] Sokal's[12] figure of 1 per cent expectancy of cancer during the lifetime of a patient with nodular goiter, which is based on his generous estimate that three fourths of these cases of cancer arise in previously nodular glands, is too high. Six of the 14 patients with nonpapillary cancers gave a history of goiter of over a year's, but only 2 of over three years' duration.

As stated above, there was 1 cancer in about 250 cases of toxic nodular goiter. Since these glands were removed for reasons not related to their physical character or size, it was believed that they would not have undergone the process of selection comparable to the nontoxic gland. During the period of study, surgery was the treatment of choice for this condition and was carried out whenever possible. For these reasons, aside from the state of function affecting the development of malignant change, the nodular toxic glands should reflect the true frequency of cancer in the glands not removed. This series is not large enough for such a figure to be derived accurately, but the stated prevalence is in approximate agreement with that obtained from the series of patients with nontoxic nodular goiter.

If the policy of removing all nodular thyroid glands was followed in this clinic, it would be necessary to operate on 3 of every 100 new patients registered. The value of such an approach to the cure of thyroid cancer would be measured in maximum terms of 1 death a year if all such cancers arose in nodular goiters. The disadvantages in terms of morbidity, rare mortality, patient resistance and increase in general cost of medical care seem to be prohibitive.

Summary and Conclusions

The removal of all thyroid nodules from patients in the Great Lakes region seems to be a medically impractical and economically unsound approach to the problem of thyroid cancer in nodular goiter.

The frequency of unsuspected thyroid cancer in the surgical series was 3.7 per cent. An approximate estimate of preclinical cancer in the nonsurgical series was 0.2 per cent and probably not over 0.4 per cent.

In this series the discovery rate of carcinoma of the thyroid gland was not reflected in the mortality statistics.

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IDIOPATHIC HYPOGAMMAGLOBULINEMIA AND AGAMMAGLOBULINEMIA*

Review of the Literature and Report of a Case

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IN 1952 Bruton[1] introduced the term "agammaglobulinemia" to describe a new syndrome. The subject of his paper was an eight-year-old boy who contracted repeated respiratory and blood-stream infections, often with the same organism. He was subsequently found to be unable to produce antibodies against pneumococcal polysaccharide, diphtheria toxoid and typhoid vaccine. Electrophoretic analysis of the plasma demonstrated virtually complete absence of gamma globulin. Since that time about 24 new cases have been reported,[2,7-11] 4 in adult men and 1 in an adult woman. An additional case is presented here, and the literature reviewed.

CASE REPORT

D.H. (U.H. 770190), a 27-year-old man, was admitted to the University Hospital on November 18, 1953, because of recurrent respiratory infections. He knew of no frequent or incapacitating illnesses in childhood, and, with the exception of what he called "influenza" at the age of 10, he had been well as a child. His illnesses dated back to 1945, when, while he was in the Army in Kentucky, a severe upper respiratory infection associated with fatigue developed. As a result he was hospitalized for 1 week. During the ensuing months, both en route to and in Europe, he was hospitalized repeatedly for similar episodes of varying severity. In April, 1945, he returned to the United States and was almost constantly hospitalized thereafter for respiratory infections. Antibacterial treatment consisted of penicillin and sulfonamides.

Since 1945 there had been 9 hospitalizations and an equal number of confinements to bed at home with chills, fever, cough, occasional hemoptysis and pleuritic pain. Just before admission to the University Hospital he had been in another hospital because of the sudden onset, at work, of a severe, sharp pain in the left side of the chest that was increased by deep respiration. His condition appeared so alarming that he was placed in oxygen at the plant dispensary and given opiates before transportation to the hospital.

On admission to the other hospital he was cold and clammy and was splinting his chest. The temperature was 100°F., the pulse 80, and the respirations 20. There was dullness at the left base. The white-cell count was 14,350, with 71 per cent neutrophils. Sputum culture was negative for pyogenic organisms. X-ray examination of the chest showed infiltration of the apex of the left lower lobe and small calcified lesions in the right hilus. He was treated with penicillin. On October 28 his lungs were clear of inflammatory lesions. On November 1 the pain in the left side of the chest subsided and shifted to the right lower aspect of the chest, where it was also pleuritic. X-ray study of the chest on November 3 revealed a new area of pneumonitis in the lower pole of the right hilus. A diagnosis of histoplasmosis was made on the basis of a ++ histoplasmin skin test and recovery of this organism from culture of the sputum. He was then referred to University Hospital for further study and treatment.

Physical examination disclosed a thin, well developed man in acute respiratory distress. Cervical and axillary lymph nodes were palpable and slightly tender. The pharynx and tonsils were not inflamed. The chest was of normal configuration. Breathing was diaphragmatic in type. There were fine rales over the entire left-lung field but no dullness to percussion. The spleen was palpable 2 cm. below the left costal margin, and the liver 3 cm. below the right costal margin. There was mild tenderness in the epigastrium to palpation. There was no cyanosis or clubbing of the extremities. The remainder of the physical examination was within normal limits.

The temperature was 102°F. by rectum, the pulse 105, and the respirations 20. The blood pressure was 105/80.

On the day of admission the hemoglobin was 14.5 gm. per 100 cc., and the white-cell count 8300, with 80 per cent neutrophils, 13 per cent lymphocytes, 3 per cent monocytes and 4 per cent eosinophils. Subsequent white-cell counts rose to 12,400 on November 23 and 14,600 on November 30, with essentially the same differential. The urine was negative for protein and sediment on November 18 and again on November 30.

The total serum protein on November 25 (Wolfson and Cohn[12] method) was 5.05 gm. per 100 cc., with albumin of 3.52 gm., globulin of 1.53 gm. and gamma globulin 0.15 gm. per 100 cc., or 3 per cent of the total protein. Tiselius electrophoresis on the same sample gave the curve shown in Figure 1. Values determined by this method were as follows: total protein 5.55 gm., albumin 3.04 gm., globulin 1.97 gm., and gamma globulin 0.02 gm. per 100 cc., or 0.4 per cent of the total protein.

Determinations of the serum van den Berg, calcium, phosphorus, Congo-red removal, prothrombin time, serum complement, thymol turbidity and uric acid were all normal. Cephalin flocculation was + in 48 hours. Serum creatinine was 0.58 mg. per 100 cc. Sternal-marrow aspiration and biopsy revealed no abnormal cells. Cultures from both marrow sources as well as culture of 5 sputum and 3 blood specimens were negative for tubercle bacilli and fungous growth. The organisms cultured from the sputum were *Streptococcus viridans, Neisseria catarrhalis* and *Haemophilus haemolyticus*. The diagnosis of active histoplasmosis that had been made in another hospital could not be confirmed bacteriologically despite 2 bone-marrow, 5 sputum and 3 blood cultures that were placed on Sabouraud's glucose-agar and blood-agar slants.

Skin tests with blastomycin, coccidioidin and old tuberculin were negative. Histoplasmin, 1:1000 dilution, caused a 1-cm. area of erythema and a 0.5-cm. area of induration in 24 hours that persisted at 48 hours. This was repeated and confirmed. Complement-fixation tests for histoplasmosis, blastomycosis and coccidioidomycosis were negative on 3 occasions.

Review of all x-ray films of the chest from 1946 to November, 1953, with the exception of those taken in 1952, demonstrated a pattern of recurrent bilateral inflammatory disease, with sparing of the apex, and, beginning in 1950, bilateral nodular parenchymal densities with calcified centers emerged. These changes were compatible with an infection with histoplasmosis acquired some time before 1950.

The patient was treated with penicillin and analgesics for a 10-day period, during which the temperature was both remittent and intermittent, reaching a maximum of 104°F. by rectum. He was discharged from the hospital 4½ weeks after admission.

At home he had another episode of chills, cough and temperature of 100.4 to 102.6°F. His physician treated him with sulfonamides and chloramphenicol, and the symptoms subsided.

On January 27, 1954, he was readmitted to the hospital and given 24 gm. of human gamma globulin intramuscularly, in the form of measles-immune gamma globulin, over a 24-hour period. Plasma samples were obtained and frac-

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tionated by filter-paper electrophoresis after the method of Kunkel and Tiselius.[12] The values for gamma globulin are graphically illustrated in Figure 2. Values of plasma samples from the patient's mother and father tested for gamma globulin by the same method were 20.2 and 17.3 per cent respectively.

During the period of injection and for 2 weeks subsequently he was asymptomatic. On February 5 he again had a temperature of 101°F., diffuse rales, chest pain and cough. X-ray study showed an inflammatory infiltration in the right upper lung. He was not treated with antibiotics, and the pneumonitis subsided spontaneously. Complement-fixation tests for mumps, influenza A' (FM 1), influenza A (PR 8) and influenza B (Lee) were negative. The blood was Type A and Rh positive, but the serum lacked antibodies to Type B cells. An attempt was made to immunize the patient against typhoid-paratyphoid vaccine. The vaccine contained 1,000,000,000 killed typhoid bacilli and 750,000,000 each of killed paratyphoid A and B bacilli. Three subcutaneous doses of 0.5 cc. were injected at intervals of 7 days. One month after the last injection a blood sample was obtained and tested for antibody; none was present.

At the conclusion of the studies a program of intramuscular injections of gamma globulin, 7 gm. (0.13 gm. per kilogram of body weight) once monthly, was started. In the past 3 months, despite this therapy, he has had 1 febrile episode similar to though milder than the previous ones, necessitating 4 days of treatment with sulfonamides and a period of bed rest. He has, with this exception, been able to work satisfactorily.

Discussion

After Bruton's[1] original paper several investigators reported additional cases in children bringing the total to about 20.[7-9] All patients were males. Young and Wolfson[10] were apparently the first to report this syndrome in 4 adult men. The cardinal features were marked depression or absence of gamma globulin, multiple infections and inability to form antibodies. These were uniformly present in the reported adults, as well as in our patient. The antibodies tested for by Young and Wolfson[10] consisted of hemagglutinins, Schick and Dick antibodies and tuberculin hypersensitivity.

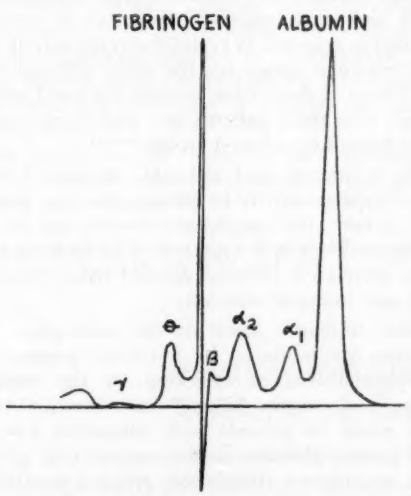

Figure 1. *Tiselius Electrophoresis Pattern on November 25 (Descending, pH 8.6, Veronal Buffer).*

Recently, the first report of this syndrome in a female was made by Sanford et al.,[11] who described its occurrence in a thirty-nine-year-old woman. Unfortunately, their study does not contain information concerning liver-function tests, proteinuria or gamma-globulin half life.

There are other diseases in which gamma-globulin levels may be secondarily and considerably diminished, such as severe nutritional deficiency,[3] the nephrotic syndrome[1,3] and idiopathic hypoproteinemia.[4-6,14,15] Each of these, however, in contradistinction to idiopathic hypogammaglobulinemia and agammaglobulinemia, has one or more of the following characteristics: edema, low total plasma proteins or albumin, proteinuria and abnormal liver function. Thus, low gamma globulin per se is necessary but not sufficient alone for the diagnosis.

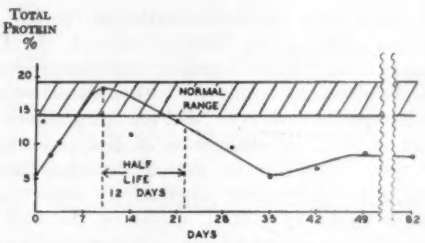

Figure 2. *Changes in Plasma Gamma Globulin after Injection of 24 Gm. of Human Gamma Globulin Intramuscularly at Day 0.*

One can see from the data presented that gamma-globulin values were determined by three different methods: chemical, Tiselius electrophoresis and filter-paper electrophoresis. The first two were done on the same specimen of blood, and their respective concentrations were 3 and 0.4 per cent of total protein. The filter-paper method was used for convenience in following the changing levels of gamma globulin after injection. Figure 2 demonstrates that the baseline value was 6 per cent of the total protein. We believe that the disparity between these values can be explained. Both the chemical and the filter-paper methods involve in their final step a colorimetric reading that, at the low concentration of gamma globulin present, is subject to considerable error. The filter-paper method is probably subject to the greatest variation in this respect because of the diffuse end point on the paper and the colorimetric error mentioned above. This method serves its purpose well, however, in following changes of gamma globulin when performed by the same person — as in the case reported. The most accurate value for gamma globulin is represented by the Tiselius value of 0.4 per cent of total protein.

Genetic control of gamma-globulin synthesis is under investigation. It will be noted that all reported cases, with the exception of 1,[11] occurred in males. Bruton et al.[2] examined the plasma of siblings, par-

ents and one set of grandparents in 2 of their cases. All were found to have normal quantities of gamma globulin. We examined the plasma of our patient's parents and found normal quantities. Young and Wolfson[10] have suggested that this syndrome may be a result of recessive sex-linked genes in homozygous males. They further divide the syndrome into two genetic types: patients with lymphopenia and absent lymph-node germinal centers[8,9] and those who have normal lymph nodes and do not have lymphopenia. The validity of this grouping remains to be confirmed.

For many years the determination of the half life of gamma globulin has been of interest. In 1952 Coursaget et al.,[16] in an ingenious experiment in rabbits, simultaneously employed both radioactive and heavy isotopes of carbon to label gamma globulin. In contrast to albumin, whose rate of disappearance is linear, they found that the rate of disappearance of gamma globulin became progressively slower with increasing time. In rabbits, therefore, the half life was initially 5 days and subsequently became 24 days. If this behavior is true of human gamma globulin, it should be noted that all the studies reported below were done in the period immediately after the administration of gamma globulin and are thus comparable.

The newborn infant possesses, as determined by immunochemical methods, a gamma-globulin half life of 30 to 35 days.[17] Dixon et al.,[17] employing an I^{131}-labeling method, found the half life in children six months to eight years to be 20.3 ± 4.1 days. Bruton and his associates[1,2] showed the half life in children with low and absent gamma globulin approximately eight years of age to be 30 and "twenty days or longer" respectively. This indicates that the half life of gamma globulin in this syndrome in children is normal. In adults, Dixon et al.[17] found the half life to be 13.1 ± 2.8 days. Figure 2, showing the calculation of the half life from our data, would place it at about 12 days — in close agreement with Dixon's values for normal adults. It can be concluded, therefore, that in these subjects with idiopathic hypogammaglobulinemia and agammaglobulinemia the rate of degradation of injected gamma globulin is normal regardless of the age group.

Homburger and Petermann[14] and Bendich and Kabat[15] described a syndrome that they called "familial idiopathic dysproteinemia" occurring in a single family. It was characterized by edema of the legs, with ulceration in males and functional vascular changes in females, a disproportion between protein components of the blood plasma, congenital malformations and a high prevalence of stillbirths. A woman in this group who had low total protein, albumin and gamma globulin was found to have a gamma-globulin half life of 3 to 5 days. This unusually short half life makes it apparent that all patients with low gamma globulin need not have the same metabolic defect.

It is interesting to speculate on the mode of survival of these patients. The advent of antibiotics has made possible the successful treatment of bacterial infections. These drugs, because of their limited specificities, however, could not explain the survival that follows a viral infection. Many alternative explanations are readily apparent. In the first place viral infections may be self limiting. Burnet[18] points out that ideally viruses live in a manner that would avoid killing the host since such an occurrence would terminate their own survival. Secondly, antibodies to infectious agents are not found in the gamma-globulin fraction exclusively. Blood-group isoagglutinins, reagins, Wassermann antibodies and typhoid O antibodies migrate between the beta and gamma fractions.[19,20] In animals antibodies to the viruses of Venezuelan and Western equine encephalitis migrate with the beta and gamma globulins.[21] Thirdly, a tissue immunity that does not depend on circulating antibody has been postulated.[22] Fourthly, extremely low levels of circulating antibody that are not detectable by current laboratory procedures may still be sufficient to eradicate some infectious agents.[23] And, finally, infection of a cell by one virus may prevent or partially inhibit "simultaneous propagation of another viral agent" in the same cell.[24]

Other reports[1,2,8,9] and the case presented above show that patients with idiopathic hypogammaglobulinemia and agammaglobulinemia fail to produce antibodies in response to typhoid vaccine despite normal or elevated values for the other globulin fractions. Other authors have pointed out (and we can confirm) that these patients also lack isoagglutinins against heterologous blood groups.[8,10,11]

It is of interest that although the skin test for delayed hypersensitivity to histoplasmin was positive in this patient, the complement-fixation test for circulating antibody was negative. This illustrates the lack of correlation between delayed tissue hypersensitivity and humoral immunity.

Recent studies,[8,9] based on the assumption that antibodies are produced by immature plasma cells and lymphoblasts, as indicated by the work of Keuning and van der Slikke,[25] have shown that the lymph nodes of patients with idiopathic low and absent gamma globulins do not respond with plasmacytosis to antigenic stimulation, giving a possible explanation for the blood protein abnormalities in this syndrome.

Another question of importance concerns etiology. We believe that the case of idiopathic hypogammaglobulinemia presented above was of an acquired rather than a hereditary type. This assumption is based primarily on the fact that symptoms began so late in life. We are also reasonably convinced, although unable to prove by our own culture methods, that this patient at one time had had histoplasmosis. Evidence for this conclusion is provided by the characteristic x-ray changes, the positive skin test and the reported positive culture in another hospital. From

the x-ray changes it appears that the initial infection occurred before 1950 and possibly in 1945. This would coincide with the onset of symptoms. Two questions arise: Could histoplasmosis and resulting infection of the antibody-forming reticuloendothelial system have resulted in permanent depression of antibody formation, or could the depressed antibody production, which was due to some unrelated factor, have made him susceptible to histoplasmosis? If the former is true, its importance could easily be established by skin tests with histoplasmin in all cases of this syndrome.

Bruton's discovery has raised a number of interesting problems in the field of immunology. It is hoped that the investigations performed on patients with idiopathic hypogammaglobulinemia and agammaglobulinemia will provide better insight into the mechanisms of antibody production and host resistance.

Summary

The syndrome of idiopathic hypogammaglobulinemia and agammaglobulinemia is described, and the literature reviewed. A case in an adult male is presented. The essential features of the syndrome include recurrent infections, greatly diminished or absent circulating gamma globulin, normal levels of other blood proteins, inability to form circulating antibodies to artificially administered antigens or infecting organisms, absence of heterologous blood-group isoagglutinins and half life for injected gamma globulin of about 20 days in children and about 12 days in adults.

Treatment consists of replacement therapy with human gamma globulin in doses of 0.1 gm. per kilogram of body weight.

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AGAMMAGLOBULINEMIA AND BRONCHIECTASIS*

A Report of Two Cases in Adults, with Autopsy Findings

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In 1952 Bruton[1] reported the first case of agammaglobulinemia in an eight-year-old boy. The absence of antibody formation was illustrated by infection with the virus of epidemic parotitis three times, failure to acquire a negative Schick test after repeated injections of diphtheria toxoid and failure to develop immune bodies after injection of pneumococcal polysaccharides and killed typhoid bacteria. The total serum protein was 6.65 gm., the albumin 4.07 gm., and the globulin 2.58 gm. per 100 cc. Electrophoretic studies showed that there was no gamma globulin. Treatment with parenteral administration of gamma globulin was apparently successful in preventing new infections. This therapy was given because immune bodies are found in the gamma-globulin fraction of plasma.[2]

After this report Janeway et al.[3] described 9 other patients, all boys, and suggested that the abnormality

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may be a sex-linked congenital defect. Intractable diarrhea in infancy, repeated infections of all types, arthritis and bronchiectasis were clinical features of the syndrome.[4] It was noted that small amounts of gamma globulin, usually less than 30 mg. per 100 cc., may be detected only by immunochemical methods. The authors used the term "agammaglobulinemia." Keidan, McCarthy and Haworth[5] presented a case of generalized vaccinia in an eight-week-old girl who never developed neutralizing antibodies to vaccinia and whose serum contained no gamma globulin by electrophoresis. Autopsy showed a striking absence of lymphocytes in lymph nodes and the spleen, to correlate with a clinical lymphopenia (count of 2 per cent). The lymphoid elements of the spleen and the follicles of the lymph nodes were composed of mononuclear cells and plasma cells. Arends, Coonrad and Rundles[6] reported agammaglobulinemia in a fifty-eight-year-old woman with malignant lymphoma, repeated severe respiratory infections and skin infections. Plasma cells were absent in a bone-marrow aspirate. Sturgis[7] described a thirty-six-year-old man who had recurrent viral and bacterial infections, and who had only a barely detectable amount of gamma globulin. McFarlane et al.[8] reported the case of a man with diffuse plasmacytosis, perhaps a variant of multiple myeloma, whose serum globulin was 5 to 6 gm. per 100 cc. All the globulin migrated at a position between beta and gamma globulin. There was no detectable gamma globulin. The patient had a chronic cough of five years' duration. Sanford, Favour and Tribeman[9] presented the case of a woman with severe recurrent infections, a transient spruelike syndrome, repeated epidemic parotitis and absent gamma globulins. She failed to develop immune bodies after injection of various antigens; the total serum protein was 4.7 gm. per 100 cc., with albumin of 4.1 gm. and globulin of 0.6 gm. per 100 cc. Her 2 sons were normal, and she had had an apparently successful smallpox vaccination as a child.

The 2 adults described below had agammaglobulinemia and severe bronchiectasis, and died after repeated respiratory-tract infections.

CASE 1.* D. F. B. (M.G.H. 640266), a 25-year-old white housewife, entered this hospital for the first time in November, 1948, complaining of a productive cough for 1 year. The only known childhood disease was varicella. She had been well until June, 1947, when, after the delivery of her 1st child, she failed to regain her usual strength. During the next 3 months a paroxysmal cough developed and soon became productive of 1½ cupfuls of thick, yellow sputum a day. In December she had bronchopneumonia and intermittent fever (maximum temperature of 101°F.). Over the next 6 months her weight fell from 112 to 92 pounds. Brief study at a sanatorium gave no evidence of tuberculosis. Because of continuing cough and debilitation she was studied at another hospital in August, 1948.†

Physical examination revealed clubbing of the fingers, and a pleural friction rub over the right middle lobe. The urine and stools were normal. The hemoglobin was 11.9 gm. per 100 cc., and the white-cell count 16,600, with a normal differential. Normal respiratory-tract floras were cultured from the sputum. The total serum protein was 5.7 gm., the albumin 4.7 gm., and the globulin 1.0 gm. per 100 cc. Bronchograms showed bronchiectasis in both lower lobes, in the right middle lobe and in the lingula of the left upper lobe. A program of aerosol penicillin and postural drainage was started, but penicillin was stopped after the appearance of a rash. With postural drainage there was decreased sputum, increased exercise tolerance and a weight gain of 14 pounds.

In November, when she entered this hospital for evaluation, she was improving and was advised to continue postural drainage.

She was readmitted to the hospital in April, 1949, for resection of the diseased segments of the lung. Repeated studies of the serum protein showed values for albumin of 4.5 to 5.0 gm. and globulin 0.91 to 1.48 gm. per 100 cc. The inferior lingular segment of the left upper lobe and all the basal segments of the left lower lobe were resected. She was discharged improved.

She was admitted to this hospital for the 3d time in May, 1951, for possible resection of the right lower lobe. In the interval, there had been 1 episode of bronchopneumonia. The previous resection had resulted in decreased sputum production and had improved her general health. Surgery was postponed because of an acute respiratory infection, and she was discharged.

In April, 1953, at the age of 30, she had her 4th admission to this hospital. In the interval she had been seen every 6 months in the clinic. Initially, she did well; however, during the year before admission, her condition deteriorated rapidly. She received intensive antibiotic and nutritional therapy for a month and was discharged.

When she was readmitted to the hospital in June her general condition was still poor, and additional therapy was given for a month. The total serum protein was 4.5 gm., the albumin 3.7 gm., and the globulin 0.8 gm. per 100 cc. The right middle and lower lobes were excised, and she was discharged in August.

Eight days later, she was readmitted to the hospital because of a pneumothorax and empyema on the right. Cultures from the chest and sputum contained *Staphylococcus aureus* and coliform bacilli. Open drainage was established, and she was given chloramphenicol. Improvement was gradual, and she was discharged.

In December readmission was necessary because of progressive dyspnea. Physical examination was as before with more marked cachexia. The hemoglobin was 14.8 gm. per 100 cc., and the white-cell count 14,600, with 89 per cent neutrophils. Sputum and empyema drainage contained alpha-hemolytic and nonhemolytic streptococci, moderate numbers of pneumococci and a few colonies of *Staph. aureus* and diphtheroids. The total serum protein was 5.5 gm., the albumin 4.2 gm., and the globulin 1.3 gm. per 100 cc. A Tiselius electrophoretic determination of the pattern of the serum proteins showed the albumin to be 53 per cent, $alpha_1$ globulin 10 per cent, $alpha_2$ globulin 13 per cent, $beta_1$ globulin 16 per cent, $beta_2$ globulin 7 per cent, and gamma globulin 1 per cent. By immunochemical technics‡ the gamma-globulin level of the serum was 54 mg. per 100 cc. (normal, approximately 11 per cent of the total protein, or 700 mg. per 100 cc.). The blood was Type A and Rh negative, and the titer of the isohemagglutinin, anti-B, was only + at a dilution of 1:4 (normal adult titer is positive at 1:16 or higher). The serum carbon dioxide was 29 milliequiv. per liter, and the vital capacity was 1000 cc. The patient was given penicillin, chloramphenicol and supportive treatment, with little improvement. On the 25th hospital day, she received 21 cc. (3.78 gm.) of human gamma globulin intramuscularly. Six days later herpes zoster developed over the right aspect of the chest. She was discharged in February, 1954, after minimal improvement.

The final admission was in March. Two weeks previously she had received an injection of gamma globulin (0.3 cc. per pound of body weight). One week later there was increased dyspnea, more profuse empyema drainage and fever. X-ray study of the chest on admission revealed a larger area of consolidation in the left-lower-lung field and increased

*Previously reported in part.[4]

†The Joseph H. Pratt Diagnostic Hospital kindly made available the clinical findings of this admission.

‡The immunochemical studies were kindly performed by Dr. David Gitlin at the Children's Medical Center, Boston.

pulmonary infiltration in the right-lower-lung field. Her cough was feeble and ineffectual. Cyanosis became marked, and she died on the 2d hospital day.

At autopsy, performed 5 hours after death, both pleural spaces were obliterated by dense fibrous adhesion. A sinus tract extended from the skin, in the right axillary line, into a cavity bounded by the diaphragm, posterior mediastinum and right lung. The cavity contained 200 cc. of green-yellow pus and communicated with the right-middle-lobe bronchus by a small tract. The bronchi were everywhere dilated and often pus filled, forming bronchiectatic abscesses. The bronchioles could be opened almost to the pleura. There was edema and emphysema in all lobes and additional bronchopneumonia in the right upper lobe. The bronchial lymph nodes were enlarged, soft and gray. The heart weighed 280 gm.; the right ventricle was 4 or 5 mm., and the left 11 mm. thick. The spleen weighed 190 gm., and the follicular markings were not seen. The remaining organs and bone marrow were normal.

Microscopical examination of many sections of the lungs revealed neutrophilic débris in the bronchiectatic abscesses and poor preservation of the bronchial mucosa. There was a dense lymphocytic infiltration, many mononuclear cells and edema with capillary dilatation about the affected bronchioles. Diffuse fibrosis was noted in the pleural, subpleural and interlobar areas, with fairly large collections of lymphocytes and mononuclear cells. No plasma cells and no pre-plasma cells were seen. The lymph nodes from the carina, lung roots and peritoneal cavity all showed a poorly defined cortex, with no follicle formation. The sinusoids were dilated and filled with large mononuclear cells. In the mediastinal lymph nodes many of these cells contained both anthracotic and hemosiderin pigments. Other mononuclear cells appeared immature, with rounded nuclei and abundant cytoplasm with a faint rim of basophilia. No mature plasma cells were seen. The liver architecture was normal; a moderate number of hepatic cells had glycogen vacuoles in their nuclei. The portal spaces contained a few lymphocytes but no plasma cells. The spleen had small lymphoid collections about the penicillate arteries, but there was no germinal-center formation. The sinusoidal cells were abundant and plump, and often contained phagocytized material. No plasma cells were observed. Sections of the stomach, duodenum, ileum, colon and rectum were examined. Lymphoid aggregates were present in each portion and were composed of many adult lymphocytes and mononuclear cells. There was no follicle formation and no plasma cells. The bone marrow of the vertebras, ribs and femur showed active myeloid cells, normal megakaryocytes, erythropoietic elements and fat. No plasma cells were seen when all the tissues were examined after methyl green pyronin staining.

The slides prepared from lung specimens in 1949 and 1953 were reviewed. In areas of severe bronchiectasis there was infiltration by lymphocytes, often in follicles with germinal centers. Only 5 plasma cells were seen in 27 sections showing severe chronic inflammation.

Case 2. D. F. (M. G. H. 709895), a 53-year-old housewife, was seen in the clinic of this hospital in August, 1950, with complaints of weight loss, diabetes mellitus and chronic cough. The only known childhood infection was pertussis. In 1922 she had had typhoid fever, pneumonia and erysipelas. She was then well until 1947, when she began to lose weight, going from 116 to 84 pounds. Diabetes mellitus was discovered in 1948, and with treatment she gained 10 pounds. Because of the onset of a chronic productive cough, she was hospitalized elsewhere in April, 1949. A diagnosis of bronchiectasis in the left lower lobe was made. In January and May, 1950, she was studied in a different hospital,* where additional diagnoses of pruritus vulvae, dermatitis factitia and psychoneurosis were made. The total serum protein was 4.9 gm., the albumin 3.8 gm., and the globulin 1.1 gm. per 100 cc. She was discharged but re-entered the 1st hospital in the same month with bronchopneumonia.

In July, 1951, she was 1st admitted to this hospital with acute pneumonia of the left lower lobe and empyema. She had been seen in the clinic during the preceding 11 months. X-ray study of the chest had shown bilateral bronchiectasis, and treatment with chloramphenicol and chlortetracycline had improved her symptoms. Eight months before admission, otitis media developed on the right, requiring paracentesis and penicillin. On admission physical examination revealed a febrile, pale, thin white woman with signs of consolidation and fluid in the left hemithorax. The empyema cavity eventually required open thoracotomy and drainage. She was discharged improved.

In October, 1952, the 2d admission was for complaints of pain in and limitation of motion of the left hip. In the interval the empyema drainage ceased, and she was treated for sinusitis and infection in a finger. Clubbing of the fingers and toes was noted 8 months before admission. Four months later, mild pain appeared in the left knee and buttock, with some swelling of the knee. Pain in the left hip developed suddenly 6 hours before admission; it was not associated with chills or fever. There was local tenderness about the left hip, buttock and thigh. The blood hemoglobin, white-cell count and differential were normal. The total serum protein was 5.4 gm., the albumin 4.3 gm., and the globulin 1.1 gm. per 100 cc. The serum calcium, phosphorus and uric acid were normal. The alkaline phosphatase was 13.1 Bodansky units per 100 cc. A bone-marrow aspirate was normal except that no plasma cells were seen. Multiple skeletal x-ray films were normal. An inguinal-lymph-node biopsy showed chronic lymphadenitis, with rare germinal centers and rare plasma cells. The patient was given physiotherapy, penicillin and a sulfonamide and was discharged 2 months later.

In January, 1954, she was readmitted to the hospital with progressive shortness of breath and cough of 2 weeks' duration. After discharge the arthritis continued to improve, and she was able to walk with crutches. In the 2 weeks before admission, her sputum had increased and she had had a dull pain in the left anterior part of the chest, especially with coughing, and a maximum temperature of 101°F. Physical examination showed a bilateral purulent conjunctivitis, and findings suggestive of pneumonia were present over the left upper lobe. There was ++ ankle edema. The blood hemoglobin was 8.5 gm. per 100 cc., and the white-cell count 5700, with 67 per cent neutrophils. The red cells were normochromic and microcytic; the reticulocyte count was 5.5 per cent. Multiple stool guaiac tests were negative. A bone-marrow aspirate was normal except for the absence of plasma cells. The serum iron was 138 microgm. per 100 cc., and the Coombs test was negative. The total serum protein was 4.4 gm. per 100 cc., with an albumin of 3.5 gm. and a globulin of 0.9 gm. per 100 cc. Filter-paper electrophoresis showed albumin of 62 per cent, $alpha_1$ globulin 12.4 per cent, $alpha_2$ globulin 14.9 per cent, beta globulins 10.7 per cent, and gamma globulin 0. The blood was Type O and Rh negative, and there were no isohemagglutinins, anti-A or anti-B. After 3 whole-blood transfusions the hemoglobin failed to rise though no hemolysins could be demonstrated. The pulmonary symptoms gradually subsided with penicillin. She was given 30 cc. of human gamma globulin (5.4 gm.) intramuscularly, without apparent change, before discharge.

In March she was readmitted to the hospital because of vomiting, which followed paroxysms of coughing. She had received 20 cc. (3.6 gm.) of gamma globulin each month since the first injection. Physical examination was unchanged. The hemoglobin was 7.5 gm. per 100 cc., and the white-cell count 4500, with a normal differential. She was given 3000 cc. of whole blood during the next month and was discharged improved.

One month later readmission was necessary because of anorexia and weakness. New physical findings were those of congestive heart failure and splenomegaly. The hemoglobin was 3.0 gm. per 100 cc., and the white-cell count 1700. The stools gave negative guaiac tests; the reticulocyte count was 1.0 per cent. There were no acid or cold hemagglutinins in the blood and no hemoglobin in the urine. After 4 packed red-cell transfusions she was discharged improved.

She returned 10 days later for her final admission. In the interval the hemoglobin had fallen from 10.7 to 5.0 gm. per 100 cc. The white-cell count was 2300, with 57 per cent neutrophils and 43 per cent lymphocytes. Bone-marrow aspirate showed erythroid hyperplasia. Penicillin and transfusions did not change her course. She became weaker and died on the 13th hospital day.

*St. Elizabeth's Hospital, Brighton, Massachusetts, which kindly made available the clinical findings of this admission.

At autopsy, performed approximately 6 hours after death, the right pleural cavity was obliterated by fibrous adhesions, and there were similar adhesions over the apex of the left lower lobe. The apexes of both lungs were noncrepitant and on cut section showed a hemorrhagic bronchopneumonia with a fine, yellow granularity superimposed on a firm, deep-red background. The bronchi and bronchioles to all lobes were diffusely dilated, and their mucosa was in transverse folds; the lumens contained copious amounts of hemorrhagic purulent material. The bronchial lymph nodes were enlarged and anthracotic. The liver weighed 1630 gm. and was normal. A single yellow crystalline stone was found in the gall bladder. The spleen, which weighed 570 gm., was deep red, soft and without discernible architecture. There was a single yellow subcapsular infarction measuring up to 9 mm. in greatest dimension. The remaining viscera and bone marrow were normal.

Microscopical examination of the lung showed numerous dilated bronchioles, often filled with neutrophils and lacking a mucosa. The peribronchial and peribronchiolar regions had numerous lymphocytes, mononuclear cells and scattered neutrophils. Subpleural, pleural and interlobar areas showed scarring, with focal collections of lymphocytes. Diffuse emphysema and moderate edema were present. No plasma cells were seen. The liver sinusoids were dilated and had prominent lining cells. The spleen was congested, with large dilated sinusoids lined by plump littoral cells. The penicillate arteries were sheathed by sparse collections of lymphocytes without germinal centers. The infarcted area contained dense fibrous tissue and hemosiderin-laden macrophages. The lymph nodes from the mediastinum and peritoneal cavity were quite similar to those in Case 1, with edema, sinusoidal dilatation, increased blood vascularity, increased lining and reticulum cells, and no plasma cells. The stomach had mild chronic gastritis, with lymphocytic infiltration and edema of the lamina propria. In all portions of the intestine the lymphocytes were in collections, but in no place were there germinal centers or plasma cells. The uterine cervix demonstrated a mild chronic inflammation, with early polypoid overgrowth of the stroma. In the inflammatory infiltrate no plasma cells were seen. The bone marrow was normal except that it had no plasma cells. The remaining organs were normal.

Discussion

In both cases the dominant features were repeated pulmonary infections, bronchiectasis and pulmonary insufficiency. Both patients had difficulty maintaining their weights, even with large caloric intakes. Case 2 had complicating diabetes mellitus, sinusitis, otitis media, conjunctivitis, arthritis of undetermined etiology and a hemolytic anemia of unknown etiology. Both cases seem to warrant the diagnosis of agammaglobulinemia, although by immunochemical technics Case 1 had a small and presumably ineffectual amount of gamma globulin. The diagnosis in each case was suspected because of a low serum globulin; this may not be present in children.[3] In children with agammaglobulinemia a syndrome resembling rheumatoid arthritis has been noted and is thought to represent synovial damage induced by repeated mild attacks of bacterial infection.[4] The arthritis in Case 2 may have been of this nature. The hemolytic anemia that Case 2 presented may have been associated with the abnormal and enlarged spleen. A recent report describes an adult with agammaglobulinemia whose anemia and leukopenia were relieved by splenectomy.[10] In some of the previously reported cases isohemagglutinins were absent.[1,3,9] Case 1 had Type A blood and an abnormally low titer of the isohemagglutinin, anti-B. Case 2, with Type O blood, had absent isohemagglutinins.

The site of antibody production is still disputed, though an increasing amount of evidence suggests that the plasma cell or preplasma cell may be this site.[11-15] In hyperimmune rabbits there is a massive plasma-cell infiltration of many organs and also hypergammaglobulinemia. With cortisone-induced regression of the plasma cells, the gamma globulin falls.[12] In children with agammaglobulinemia, after injection with an antigen, the regional lymph nodes showed no germinal-center formation, no plasma or preplasma cells and no antibodies.[15] Lymph nodes removed from normal children at herniorrhaphy after injection with an antigen demonstrated germinal-center formation, plasma and preplasma cells and antibodies.[15] In the cases reported above, all the lymph nodes examined and the spleen, as well as the lymphoid aggregates in the intestines, were marked by absence of germinal centers and plasma cells. However, in tissues removed surgically, at least a year before death in each case, there were rare plasma cells. The case of Keidan et al.[5] raises the possibility that the agammaglobulinemia and subsequent infections are related to absence of lymphocytes. However, in some previously reported cases and those presented above, the absence of plasma and preplasma cells, agammaglobulinemia and multiple infections seem to be related phenomena.

The diagnosis in adults may be suggested by repeated severe respiratory-tract infections, bronchiectasis and a low serum globulin. In children and adults one finds repeated infections with the same viral or bacterial agent, absent or low immune responses to vaccination or inoculations and absent or low titers of isohemagglutinins. Early diagnosis is desirable since human gamma globulin may be specific and uniquely successful when other measures fail. Cases of severe bronchiectasis seem to warrant investigation for the presence of this syndrome.

Summary

Two autopsied cases of agammaglobulinemia are reported. Both patients were women with bronchiectasis.

At autopsy, lymphoid structures had no germinal centers, and no plasma cells could be found in any tissue. The possible relation of these findings and agammaglobulinemia is discussed.

Reported cases are reviewed, and the usual clinical features are described.

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A STUDY OF THE CLINICAL REACTIONS TO VENOUS ANGIOCARDIOGRAPHY*

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THE rapid advances in cardiac surgery during the past ten years have increased the need for accurate diagnosis of lesions of the heart and great vessels. This has resulted in an ever-increasing use of the technic of angiography.

The contrast agents employed in angiography contain iodine in amounts varying from 50 to 66 per cent of their weight; they are directly irritating to living tissue,[1,2] and all are markedly hypertonic — for example, 70 per cent Diodrast (iodopyracet) has nine times, 75 per cent Neo-Iopax (sodium iodomethamate) has ten times, and 70 per cent Urokon (sodium 3 acetylamino-2, 4, 6-triiodobenzoate) has eight times the osmotic pressure of plasma. For these reasons one would expect to find frequent untoward reactions in persons receiving rapid injections of these materials. Many such reactions have been reported. Common symptoms are metallic taste, a sensation of intense heat, headache, sweating, palpitation, weakness, nausea and vomiting.[3] Pallor, flushing of the face, tachycardia, bradycardia, lowering of the systemic blood pressure[4-6] and the development of electrocardiographic abnormalities[7,8] are frequent objective reactions of the cardiovascular system. Changes in the respiratory movements have been reported,[1] as have various neurologic abnormalities,[9,10] especially when the concentrated contrast medium goes undiluted into the cerebral vessels. Thrombophlebitis has been observed proximal to the site of injection.[11]

A certain mortality associated with the procedure[12-14] has been considered to be more common with larger doses of the contrast agent, in the younger age groups and in patients with cyanosis.[12] It has been thought that some of the deaths were due to a sensitivity to the agents used. Morgan[13] noted that all the fatal cases in his series were in patients with valvular or central obstruction to pulmonary flow.

Since there has been no exact evaluation of the reactions to the rapid injection of contrast mediums and since there is no agreement about the more important factors of their production, the present study has been made in an attempt to evaluate these factors.

MATERIAL

One hundred and twenty patients were selected from a total of 300 cases subjected to venous angiography between June, 1946, and June, 1954, at the Stanford Hospital. About a fourth of the patients were chosen because they had received a general anesthetic, and the remainder were selected at random from the files. Since general anesthesia was used largely in children, the cases analyzed included a greater proportion of children than the total number of patients receiving angiograms.

Fifty-eight of the 120 patients were female, and 62 were male. The ages varied from five days to sixty-eight years. As shown in Table 1, the age distribution of patients receiving each of the three contrast agents was similar except that very few of the youngest age groups received Neo-Iopax and only 1 of the oldest age groups received Diodrast. A large variety of cardiac lesions was represented, 77 of the patients being cyanotic, and 43 being acyanotic. The type of cardiac lesion in relation to the contrast agent used is shown in Table 2. It can be seen that the distribution of cyanotic and acyanotic lesions was similar for each agent.

General anesthesia was given to most patients under the age of twelve years, and local anesthesia was used in most patients over twelve. The following anesthetic agents were used: ether (open-drop method), divinyl ether (open-drop method), nitrous oxide, Avertin (tribromoethanol) by rectum, Pentothal (thiopental sodium) intravenously and Surital (thiamylal sodium) by rectum. Avertin was given in an average dose of 88 mg., Pentothal 37 mg. and Surital 40 mg. per kilogram of body weight. Pre-

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medication varied according to the type of anesthesia the patient received. If general anesthesia was given, premedication usually consisted of scopolamine (ranging in dose from 0.008 to 0.019 mg. per kilogram of body weight) and morphine sulfate (ranging in dose from 0.12 to 0.28 mg. per kilogram of body weight). In the older children and adults when only local anesthesia was used, the premedication usually consisted of either pentobarbital alone, in a dosage of 50 to 220 mg., or pentobarbital in combination with morphine, in a dosage of 16 mg., or Demerol (meperidine hydrochloride), in a dosage of 75 mg.

The three contrast mediums were 70 per cent Diodrast (52 cases), 75 per cent Neo-Iopax (44 cases) and 70 per cent Urokon (24 cases). Table 3 shows the range of dosage and number of patients receiving each dosage.

The various reactions were obtained from the clinical records of the 120 patients studied as written by the house officer and anesthetist. We realize that this is not as satisfactory as personal observation, but we believe that with few exceptions the data are accurate, especially those concerning the more severe reactions. The actual total number of reactions may have been larger than the number reported since minor reactions may have been overlooked or not noted on the chart.

TABLE 1. *Age Distribution of 120 Patients Receiving Contrast Mediums in Relation to Agent Used.*

AGE	PATIENTS RECEIVING DIODRAST	PATIENTS RECEIVING NEO-IOPAX	PATIENTS RECEIVING UROKON
< 3 mo.	6	0	1
3 mo. - 1 yr.	8	2	5
1 - 5 yr.	16	22	8
6 - 10 yr.	8	8	1
11 - 30 yr.	13	5	4
31 - 50 yr.	1	4	2
>50 yr.	0	3	3
Totals	52	44	24

TABLE 2. *Type of Lesion in Relation to the Contrast Agent Used.*

TYPE OF LESION	PATIENTS RECEIVING DIODRAST	PATIENTS RECEIVING NEO-IOPAX	PATIENTS RECEIVING UROKON	TOTALS
Cyanotic:				77
Tetralogy of Fallot	21	18	9	
Great-vessel deformity	11	7	3	
Miscellaneous	1	4	3	
Acyanotic:				43
Patent ductus arteriosus	2	2	0	
Pulmonary stenosis	6	2	0	
Coarctation	3	0	2	
Pulmonary hypertension	2	2	0	
Superior-vena-cava obstruction	0	2	0	
Miscellaneous	4	4	5	
Normal heart (extracardiac disease)	2	3	2	

FINDINGS

Only 31 (26 per cent) patients had no untoward reaction of any kind. Since most of the unanesthetized persons had an unusual taste in the mouth and a warm sensation, these were not considered untoward reactions. Of interest is the fact that although only 15 per cent of the patients receiving Diodrast and 24 per cent of those receiving Neo-Iopax had no untoward reaction, 50 per cent of the patients receiving Urokon had no untoward reaction of any sort.

For the purposes of this evaluation it was considered that any of the following symptoms and signs constituted a mild reaction: hyperpnea, irregular respiration, cough, tachycardia, bradycardia, nausea and vomiting, urticaria and drowsiness. Since these reactions are fairly innocuous, since some of them were late in appearance and since others could have been due to the premedicating drugs or anesthesia, the patients with only mild reactions and those with no reactions were placed in the same group. A total of 81 (68 per cent) cases were thus classified.

TABLE 3. *Dosages of Various Contrast Agents.*

DOSAGE	PATIENTS RECEIVING DIODRAST	PATIENTS RECEIVING NEO-IOPAX	PATIENTS RECEIVING UROKON
cc./kg. of body wt.			
0 - 0.9	17	16	9
1.0 - 1.9	22	22	10
2.0 - 3.6	13	6	5
Totals	52	44	24

The symptoms and signs that were considered to constitute severe reactions were as follows: apnea, laryngeal spasm, Cheyne–Stokes respiration, cardiac arrhythmias, shock, pulmonary edema, convulsion, syncope and prolonged mental confusion. Deaths have been included as a severe reaction. Severe reactions developed in 39 (32 per cent) patients, some of whom had multiple evidences of difficulty.

It is of interest to see how the severe reactions correlated with various factors, such as the agent used, the dosage given, the age of the patient, the presence of cyanosis, premedication and anesthesia.

There was a striking difference between the agents. One severe reaction, a death, occurred among the 24 patients receiving Urokon, a rate of 4 per cent, as compared with 32 per cent severe reactions for Neo-Iopax and 46 per cent for Diodrast.

There is an apparent relation between the larger dosages (in terms of body weight) of Diodrast and

the severe reactions. A dose of Diodrast smaller than 1 cc. per kilogram of body weight led to only 18 per cent severe reactions whereas 1.0 to 1.9 cc. and 2.0 to 3.66 cc. per kilogram led to 59 per cent and 61 per cent severe reactions respectively (Table 4). This relation was not apparent among the patients receiving Neo-Iopax, all dosage ranges showing about the same percentage of severe reactions. Urokon caused 1 death after a total dose of 3.6 cc. per kilogram of body weight (Case 4), but no other severe reactions occurred in the group of 24 patients receiving this preparation.

No correlation could be made between the materials used for premedication and anesthesia and the number of severe reactions, although some of the milder reactions such as nausea and vomiting, flush, urticaria and somnolence were probably due to these agents.

TABLE 4. *Reactions and Deaths with Three Dosage Levels of Contrast Agents.*

Dosage Range	Total Patients Receiving Dosage			Patients with Mild or No Reactions			Patients with Severe Reactions			Deaths		
	Dio-drast	Neo-Io-pax	Uro-kon	Dio-drast	Neo-Io-pax	Uro-kon	Dio-drast	Neo-Io-pax	Uro-kon	Dio-drast	Neo-Io-pax	Uro-kon
cc./kg. of body wt.												
0.1 - 0.9	17	16	9	14	12	9	3(18%)	4(25%)	0	0	0	0
1.0 - 1.9	22	22	10	9	14	10	13(59%)	8(36%)	0	1	0	0
2.0 - 3.6	13	6	5	5	4	4	8(61%)	2(33%)	1(20%)	0	0	1

The age of the patient also showed an apparent correlation with the severe reactions, younger patients having a definitely higher percentage of reactions with Diodrast and possibly with Neo-Iopax (Table 5). However, when the dosage of the agent is related to age, it becomes apparent that the severe reactions were also related to the fact that the younger age groups tended to receive a much larger dose of the agent per kilogram of body weight (Table 6).

In relating the severity of the reaction to the presence of cyanotic congenital heart disease, there was an apparent increase in severe reactions with cyanosis, 38 per cent of patients with and 23 per cent of those without cyanosis having severe reactions. Here again, however, more cyanotic patients (72 per cent) were in the younger age groups (below five years) and therefore received larger doses of the agents; only 30 per cent of those without cyanosis were below five years of age, and this group therefore tended to receive smaller doses.

TABLE 5. *Severe Reactions in Various Age Groups.*

Age	Reactions Among Patients Receiving Diodrast	Reactions Among Patients Receiving Neo-Iopax	Reactions Among Patients Receiving Urokon
	%	%	%
< 3 mo.	83	—	—
3 mo. - 1 yr.	71	50	20*
1 - 5 yr.	56*	41	—
6 - 10 yr.	13	38	—
11 - 30 yr.	23	—	—
31 - 50 yr.	—	50	—
>50 yr.	—	—	—

*Includes 1 death.

Multiple injections of Diodrast or Neo-Iopax were given in 6 cases. Four of these patients had only mild reactions with the second injection, but 2 had extremely severe reactions with second and third injections, after having had only mild reactions to the first. One was an adult with pulmonary hypertension who, after his third injection of Neo-Iopax, manifested apnea, cyanosis and shock and remained in a critical condition for about six hours before recovering. The second was a small child who, after the second injection of Diodrast, had apnea and required artificial respiration for several minutes before ultimate recovery. It is of further interest that double injections were used in 11 of the 23 patients receiving Urokon. Only 1 severe reaction, a death, occurred in this group.

TABLE 6. *Relation of Dosage* to Age.*

Age	Patients Receiving 0-0.9 Cc./Kg. of Body Weight	Patients Receiving 1.0-1.9 Cc./Kg. of Body Weight	Patients Receiving 2.0-3.6 Cc./Kg. of Body Weight
< 3 mo.	—	2	5
3 mo. - 1 yr.	2	3	10
1 - 5 yr.	3	32	11
6 - 10 yr.	6	10	1
11 - 30 yr.	18	4	—
31 - 50 yr.	7	—	—
>50 yr.	6	—	—

*Refers to all 3 contrast agents used.

A final point of interest is that in 2 patients with obstruction of the superior vena cava severe thrombophlebitis of the entire external venous system developed after the injection of the contrast medium. In both, the agent used was Neo-Iopax. The slow venous flow in the distended veins and the resulting prolonged contact of the contrast material with the vessel walls were probably important factors in the development of the thrombophlebitis.

Deaths

In the series of 120 cases presented in this paper, 2 deaths occurred, a mortality of 1.7 per cent. A total of 6 deaths followed angiocardiography out of a total of 300 cases in this hospital during a six-year period, a mortality of 2.0 per cent. This is comparable to that reported by some authors[13,14] although it is somewhat higher than the figure given by Dotter and Jackson,[12] who listed 1 death among 397 angiocardiographic studies performed in the United States and Canada, and 1 in 59 in Great Britain. The lower mortality in the North American series was probably due to the wider use of the procedure in adults and to its performance in conditions other than congenital heart disease. To analyze the important factors, closer examination of the deaths occurring in this institution seems worth while. Cases 1 and 4 have been included as severe reactions in the data on 120 cases surveyed in this paper. The other 4 deaths occurred in 180 cases not studied in detail.

Case 1. A 29-month-old girl with cyanotic congenital heart disease had frequent attacks of extreme cyanosis. Her condition had deteriorated markedly in the few weeks before angiocardiography. Two sensitivity tests with intravenous injections of Diodrast were performed before the procedure, with negative results. No medication preceded the rectal administration of Avertin. About 1.5 cc. of 70 per cent Diodrast per kilogram of body weight (12 cc.) was injected. After the procedure the child never became fully conscious; 6 hours later bowel bleeding, and 12 hours later respiratory distress developed, leading to apnea and cardiac arrest.

Autopsy revealed defects of the interventricular and interatrial septums, malformation of the great veins and, in addition, a large thrombus extending through the septal defect and firmly attached to the atrioventricular valves. This thrombus was ante mortem and not due to angiocardiographic procedure, as shown by the fact that it could be visualized in the angiograms and on pathological examination. No cardiac catheterization had been performed before the angiogram.

Case 2. A 4-year-old boy had experienced transient cyanosis at birth, with subsequent dyspnea on exertion. Physical and mental development had been slow, and a clinical diagnosis of mongolism had been made. His condition was satisfactory before the procedure. A Diodrast sensitivity test was performed, with negative results. Premedication consisted of morphine sulfate, 3.0 mg., and scopolamine, 0.2 mg. Avertin (90 mg. per kilogram of body weight) by rectum and nitrous oxide anesthesia were used. About 1.8 cc. per kilogram (30 cc.) of 70 per cent Diodrast was injected for the angiogram. Five minutes later cardiac arrest developed, followed shortly by respiratory arrest.

Autopsy demonstrated a hypertrophied left ventricle and hypertrophy and dilatation of the right ventricle. The final diagnosis was congenital idiopathic hypertrophy of the heart.

Case 3. A cachectic, severely ill 61-year-old man presented evidence of a large mediastinal mass, obstruction of the superior vena cava and several pulmonary infarctions.

Small doses of Demerol and a barbiturate were the only premedication. Approximately 0.6 cc. of 75 per cent Neo-Iopax per kilogram of body weight was injected for the angiogram. He seemed to tolerate the procedure fairly well but subsequently became drowsy. About 3½ hours later cyanosis and rales in the chest developed, and the blood pressure fell to shock levels. In spite of supportive measures, he rapidly failed and died 10 hours after the angiogram.

Autopsy revealed a carcinoma of the right main bronchus, with extension into the superior vena cava and right atrium, metastases to the mediastinal lymph nodes and left adrenal gland and several recent pulmonary infarcts.

Case 4. A 6½-month-old male infant had congenital heart disease and episodes of severe cyanosis. Three weeks before examination a diagnosis of bronchopneumonia had been made. Subsequently, myocardial failure was diagnosed and he was placed on digitalis. During the 3 days before angiocardiography, the fluid intake had varied between ¼ and ⅓ of the optimal level for an infant of this size. After premedication of 0.15 mg. of scopolamine and ether anesthesia, 2 injections of 1.8 cc. of 75 per cent Urokon per kilogram of body weight (10 cc.) were given during the angiocardiographic procedure. The patient had no immediate reaction but was found extremely cyanotic and moribund 5 hours later. Respiration ceased shortly thereafter.

Autopsy demonstrated complete transposition of the great vessels, a single functioning right ventricle and a rudimentary left ventricle.

Case 5. A 13-week-old female infant was apparently normal until the age of 8 weeks, when a persistent cough developed. Cardiac failure was diagnosed, and digitalis given. After premedication with atropine, 0.1 mg., and nitrous oxide and ether anesthesia, an injection of 2.3 cc. of 70 per cent Urokon per kilogram of body weight (10 cc.) was given, followed in a few minutes by an injection of 1.6 cc. per kilogram (7 cc.). No immediate reaction was noted, but 1 hour after the procedure, the patient became cyanotic, froth appeared in the mouth, and lateral nystagmus was present. Three hours later respirations slowed and a few minutes later ceased.

Autopsy demonstrated congenital heart disease, with marked hypertrophy of the right ventricle, focal endocardial fibrosis, a patent ductus arteriosus and petechial hemorrhages and congestion of the lungs.

Case 6. A 10-day-old male infant had cyanotic congenital heart disease. Extreme cyanosis had been present almost since birth. After premedication of Seconal, 32 mg., and without any other anesthesia, an injection of 2.3 cc. of 70 per cent Urokon per kilogram of body weight (7 cc.) was made. No immediate reaction to the procedure was noted. Two hours after the procedure, a grunting type of respiration rhythm developed, and 3 hours after the study, respiration ceased, followed by a cessation of heart beat.

Autopsy demonstrated an aberrant left superior vena cava entering the left atrium, a large functional single ventricle, dextroposition of the aorta, pulmonary atresia and a patent ductus arteriosus.

Only 1 of these 6 patients died immediately after the injection of contrast medium. The other 5 deaths occurred three to twelve hours after the procedure had been completed. This delay and the fact that the child who died immediately had shown a negative sensitivity test to Diodrast before the procedure suggest that these deaths were not "unusual" or sensitivity reactions to the agents.

Respiratory failure was the cause of death in 4 of the late cases, shock in the fifth and cardiac arrest the mechanism in the child who died immediately after the injection.

It seems that the toxic effects of the agents were primarily responsible for death in these cases. However, it should be noted that the doses varied from a relatively small dose (0.6 cc. per kilogram of body weight) in 1 to a large dose in 3 patients receiving Urokon. Many* patients, of course, received still larger doses without death and, occasionally, without severe reactions. The poor general condition of 5 of the 6 patients (Cases 1, 3, 4, 5 and 6) was probably a major contributing factor. It has been shown that with injection of concentrated contrast mediums great decreases in blood pressure occur, owing to peripheral vasodilatation,[15] depression of the myo-

cardium[15] and striking changes in the plasma volume that are due to the osmotic and irritative properties of the agents.[16] A normal heart and circulatory system may easily tolerate such alterations, which may, however, cause death in a patient with a cardiovascular system that is already in poor condition.

Discussion

This study suggests that with doses of Diodrast or Neo-Iopax suitable for angiocardiography a certain percentage of severe reactions is unavoidable. Since most of the reactions occurred within twelve hours of injection, it is likely that they were due to the direct action of the contrast medium.

With Diodrast and Neo-Iopax severe reactions tended to appear in increasing number with higher doses of the agent (in terms of body weight), with the presence of cyanosis and in younger patients. Although it is impossible to say that any of these factors is the single cause of severe reactions, there is evidence that the dose is quite important. Studies[1,16] on normal dogs have shown that doses (or equivalent) of 1 cc. of 70 per cent Diodrast or 75 per cent Neo-Iopax per kilogram of body weight are well tolerated, whereas doses of 2 cc. per kilogram or over are almost always fatal. Although such dosage levels cannot be transferred directly to the human subject it seems likely that, once the toxic range of the agent has been reached, increasing doses are responsible for increasing numbers of severe reactions.

Urokon, in contrast to Diodrast and Neo-Iopax, seems to be relatively free of severe immediate reactions even after two or more rapid injections in some cases. In view of this apparent lack of toxicity, the studies on dogs are of great interest. It has been reported that dogs will tolerate without death, although with convulsions, a rapid injection of 5 gm. of Urokon per kilogram of body weight.[17] This laboratory has demonstrated that dogs will tolerate up to 4 cc. of 70 per cent Urokon per kilogram with only minor respiratory and electrocardiographic changes.[16] Although this apparent lack of severe reactions to Urokon and its low toxicity in animal studies seem to make it the agent of choice for this procedure, the fact that 3 late deaths have followed its use suggests that caution be used regarding expressions of its ultimate safety. More data are needed in this connection.

Summary

Reactions to the rapid intravenous injection of Diodrast (iodopyracet), Neo-Iopax (sodium iodomethamate) and Urokon (sodium 3 acetylamino-2, 4, 6-triiodobenzoate) are reported in 120 cases in which diagnostic venous angiocardiography was performed.

Severe reactions were more frequent after the use of Diodrast and Neo-Iopax than after that of Urokon. Severe reactions appeared more frequently with larger doses, in younger patients and in patients with cyanosis due to right-to-left intracardiac shunts. Of these three factors the size of the dose appeared most important.

Multiple injections of contrast medium appeared to cause more severe reactions than a single injection.

Six deaths occurred among 300 patients, a mortality of 2 per cent.

Deaths occurred after the administration of all three contrast agents. Three followed the use of Urokon. Five of the 6 patients who died were in poor clinical condition. Four had severe congenital cardiac malformations; 1 patient with metastatic carcinoma had an obstruction of the superior vena cava, and 1 child had idiopathic cardiac hypertrophy with congestive heart failure.

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MEDICAL PROGRESS

CLINICAL PULMONARY PHYSIOLOGY (Concluded)*

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BRONCHOSPIROMETRY

Bronchospirometry, the simultaneous and separate recording of ventilation and gas exchange of the two lungs, was first performed in man with the double bronchoscope of Jacobaeus and his associates.[207] A number of clinically informative results were obtained,[129] but the procedure was not generally accepted until pliable, double-lumen catheters simplified the examination and made it more agreeable to patients.[208,209] These rubber catheters have separate tubes for the two lungs within a single sheath. The airways are isolated from each other and from the atmosphere by inflatable rubber cuffs. Intubation is accomplished by indirect laryngoscopy under topical anesthesia; proper placement is assured by fluoroscopic observation, and respiratory excursions are recorded by twin spirometers.[34,129] Technical discussions of instrumentation are available.[129,210-212]

Correct interpretation of the double spirogram requires certainty concerning the catheter's position, tracings of good quality and, most important, information about over-all functional performance because bronchospirometry itself indicates only the relative functional contribution of each lung since artificial conditions due to anesthesia and intubation invalidate measurements of actual and maximal performance.[18,212] In selected cases bronchospirometry can be more helpful than any other diagnostic procedure in the clinical management of pulmonary problems. Yet no other examination has caused as much technical difficulty, and no other test has been more flagrantly misinterpreted. Difficulties are most often due to incorrect tube placement, accumulation of secretions[212] or resistance breathing.[18] Therefore, most recent developments concerned with catheter design have emphasized larger airways for freer breathing and to facilitate removal of secretions.[213-215] The new Carlens[213] catheter has a rubber hook, designed to engage the carina, which at times facilitates correct positioning, and this catheter can be placed without fluoroscopic control.

The literature dealing with bronchospirometry has been reviewed in detail during the past year.[216] The very first split-function studies made it clear that the static, two-dimensional picture of the roentgenogram does not always portray actual functional distribution, and this fact is now generally recognized.[217] Similarly, fluoroscopic and thoracometric measurements were shown to be misleading at times because the diseased lung may be adequately ventilated and yet contribute little to oxygen uptake.[129,207,218]

The right lung normally provides 50 to 65 per cent of the total ventilation, oxygen uptake and vital capacity.[120,212,219,220] Other subdivisions of the total lung capacity are similarly distributed.[72] Blood flow through the two branches of the pulmonary artery is proportional to the division of oxygen uptake provided that there is no hypoxemia.[221,222] The increased pressure in the pulmonary artery during exercise appears to be sufficient to maintain the percentage distribution of blood flow and oxygen uptake of each lung even if function is quite asymmetric.[223] A maneuver recently suggested involves occlusion of the left or right branch of the pulmonary artery with a balloon at the tip of a cardiac catheter.[224,225] This procedure, which promptly eliminates oxygen uptake on that side, has been proposed as a test of the patient's ability to survive with a single lung.[226] It appears to me that the concomitantly obtained angiocardiograms[227] are of greater diagnostic value than the physiologic observations during occlusion. There has been much speculation concerning the effect of body position on blood flow in the pulmonary artery. Bronchospirometry affords convincing evidence that a shift of flow from the upper to the lower lung occurs on changing from the supine to the lateral decubitus position.[228-230] Results of differential bronchial catheterization[231] or differential bronchospirometry[232] between the upper and lower lobe in the upright and supine position in patients after opposite pneumonectomy support the hypothesis that little blood reaches the most apical portions of the lung in the upright position; the same observation has been made by intubation with a triple-lumen catheter[233]; these data have obvious bearing on the apical localization of pulmonary tuberculosis.

Studies involving alteration of the gaseous environment of a single lung have led to the conclusion that local pulmonary circulation is controlled by the partial pressure of oxygen and carbon dioxide in the corresponding lung region,[34,222,234] an important contribution to understanding of the pulmonary circulation. The bronchospirometric technic has been used to study the mechanics of the human mediastinum. Recent experiments have shown that this is a more mobile structure than is generally believed: there is a marked reduction of the volume of the opposite lung during induction of pneumothorax,[235] and a lung can be ventilated to a normal extent solely by the swinging action of the mediastinum during electrophrenic respiration of the opposite lung.[236]

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Bronchospirometry before and after chest surgery permits measurement of functional changes of the involved lung as well as observation of the compensatory mechanism of the opposite lung.[219] Demonstrations of the marked loss of function during intrapleural pneumothorax[165,235,237] with an uncertain functional outcome after its abandonment,[219] of the function-sparing character of extrapleural pneumothorax,[57,165] of the greatly variable effects of conventional thoracoplasty,[77,165,219,238] and of the better functional results with extraperiosteal plombage procedures[238] all have materially influenced the recent choice of collapse procedures.[167] Restoration of function after pulmonary decortication has received increasing attention, and indications for this operation are now guided more by bronchospirometric findings than by roentgenograms.[239-241] After lobectomy and segmental resection complicating atelectasis, hemothorax, fibrothorax and empyema are more important determining factors in functional results than the extent of the resection itself. Few generalizations are possible concerning the bronchospirometric results in diffuse disease. Pleural involvement usually has a deleterious effect, and the chest roentgenogram leads to an unduly optimistic estimate of the function of the involved lung. In contrast, parenchymal disease must be well advanced to cause measurable asymmetry of function, and often the damage is not as great as the roentgenogram suggested.[129,219,242] Oxygen uptake on the diseased side is almost always reduced earlier and more severely than ventilation.[218,219,242]

Indications for bronchospirometry have been outlined,[218] but the range of usefulness of the procedure is so wide that a listing must always remain incomplete. At present most studies are being performed in the course of clinical research. Eventually, the procedure will find its widest application in the field of clinical evaluation. Split-function studies are most important before operation in the face of extensive disease or previous surgery and before transthoracic procedures in patients with unrelated pulmonary lesions. Estimation of the effect of anomalies or injuries of the pulmonary arteries may be mentioned as the most recent indication.[243,244]

Intrapulmonary Distribution of Gas

The intermediary step in the transfer of gases between the ambient air and the blood is the distribution of inspired air to the various parts of the lungs. This "alveolar ventilation" is affected by tidal volume, respiratory rate, volume of functional residual capacity, respiratory dead space and the uniformity of "intrapulmonary gas mixing." Uniform mixing implies that all alveoli simultaneously receive gas of the same composition and the same volume in relation to their preinspiratory volumes, that this gas mixes instantly with the functional residual gas and that there is a uniform turnover rate for all alveoli.[245,246]

The clearance of pulmonary nitrogen during oxygen breathing can be used as an index of over-all efficiency of alveolar ventilation[3,103,120] and, to some extent, of the evenness of intrapulmonary mixing.[72,246-249] During inhalation of pure oxygen the functional residual gas, which originally contains 80 per cent nitrogen, is progressively washed out. Poorly ventilated areas are rinsed more slowly, delaying complete flushing. Also, certain alveolar samples later during the flushing period may contain more nitrogen than earlier ones. A breath-to-breath record of the fall in alveolar nitrogen can be obtained with the nitrogen meter[103,120] or with a mass spectrometer.[246,249] In normal subjects the alveolar nitrogen is reduced from the normal 80 per cent to 13 per cent in one minute and to less than 2 per cent in five minutes.[3]

A simple form of this test is commonly used as a rough measure of the evenness of alveolar ventilation. The lungs are flushed with oxygen for seven minutes; the nitrogen percentage of an end-expiratory alveolar sample obtained at the end of this period is called the "index of intrapulmonary mixing."[250] This test has been criticized because the alveolar ventilation, and hence the residual nitrogen, are affected not only by intrapulmonary mixing but also by the magnitude of ventilation, functional residual volume and dead space[3,245]; the test is said to be insensitive to slight deviations from the normal, and the oxygen breathing is said to emphasize differences between normal subjects and patients because it may increase ventilation in normal persons and decrease it if there is respiratory acidosis[3]; finally, there has been some difficulty in collecting an alveolar sample in dyspneic patients and in patients with small expiratory reserve volumes.[2] Simple changes in technic, such as the use of an alveolar trap, overcome technical objections.[57] Factors other than intrapulmonary mixing that alter alveolar ventilation are not unknown variables because the functional residual volume and minute ventilation are determined simultaneously with the mixing index.[250] In a recent study of 62 normal subjects the average "mixing index" was only 0.98 per cent and never more than 1.5 per cent whereas in 42 patients with pulmonary emphysema the residual nitrogen was always more than 3 per cent, averaged 5.78 per cent and was as high as 30 per cent in the presence of complicating bullae and blebs.[72] If the upper limit of normal for the pulmonary mixing index is reduced from 2.5[250] to 1.5 per cent, the boundary between the normal state and pulmonary disease is as distinct as that obtained with the single-breath test.[57,72,79] Despite the simplicity of the test, it is a valuable index of the rapidity with which the functional residual volume is replenished with inspired gas, and it gives some indication of the effectiveness of intrapulmonary gas mixing.

The mixing problem can be approached directly by examination of the expired air after a *single* inspiration of a "foreign" gas. After expiration the gas first exhaled is pure "foreign" gas as long as the dead

space is being flushed; then, the concentration of "foreign" gas diminishes rapidly; if a horizontal plateau of alveolar gas concentration is reached, the distribution within the lung has been perfectly even.[251] If, early during the alveolar phase, there is more inspired reference gas than later, or if the plateau is uneven, this can be attributed to delivery of expired gas from regions of the lung with different end-inspiratory concentrations.[251]

At first, single-breath studies were made with hydrogen[31,252-255] or helium[256] and required fractional sampling of alveolar gas. Recently, the use of oxygen as the reference gas[74,245,257,258] and automatic, continuous and simultaneous recording of nitrogen concentration[111] and volume flow[176] of the expired gas have facilitated extensive investigations of distribution. These new methods are quite sensitive, and results are not affected by variations in tidal volume, respiratory rate and functional residual capacity. Methods for measuring the uniformity of alveolar ventilation, regardless of pulmonary blood flow, have recently been reviewed by Rauwerda[257] and Fowler.[251]

Clinical application of single-breath methods is limited at present because apparatus for fractional alveolar sampling or continuous analysis of alveolar gas is difficult to obtain and to standardize and is very expensive. With proper precautions simpler methods are almost as sensitive and clinically more applicable.

Closed systems have also been used for mixing analysis. The functional residual gas is brought into equilibrium with a known volume and concentration of hydrogen,[56] helium[70,259,260] or oxygen[247,261,262] by rebreathing into a spirometer. The time course and regularity of the equilibration process is followed by intermittent analysis of the expired gas. A delay in complete equilibration or variations of the concentrations indicate uneven intrapulmonary mixing. Unlike the single-breath methods, the equilibration technics are affected by alveolar ventilation and functional residual volume. An increase in the dead space has the same effect as uneven ventilation; by assuming perfect mixing, one can calculate the dead space, and if it appears too large, one can assume that mixing has been uneven.[56,247,248] These methods take time, are difficult and are objectionable on certain methodical and theoretical grounds.[3,248] The highly diffusible hydrogen or helium may alter the process of mixing; the rate of diffusion of these gases into the blood stream is undetermined. Simple equilibration curves can be obtained incidentally during determinations of residual volume by the rebreathing method.[56,70,247,262] The interpretational limits of these clinically useful but physiologically complex tests must be considered.

Continuous automatic analyses have demonstrated nonuniform alveolar ventilation in normal subjects.[251] Parts of the alveolar gas are ventilated only 70 to 80 per cent as well as others.[242,255] An increase of the functional residual capacity,[246,251,257] breath holding,[257] advancing age,[74,112,246,247] recumbency[257] and the lateral decubitus position[52,129,219] further the unevenness of pulmonary ventilation. Sequential distribution (which brings merely dead-space gas to the earliest filling alveoli), unequal distribution of the inspired volume in relation to the preinspiratory volume and failure of intra-alveolar mixing or layering have been mentioned among the causes of uneven distribution.[251]

Uneven ventilation may contribute to disability in patients with pulmonary disease. Parenchymal lesions reducing the distensibility of some lung regions cause local underventilation. Partial obstruction of bronchi interferes with rapid ventilation and leads to poor aeration. Selective loss of elasticity alters the timing of emptying. That the last two situations may interfere with local ventilation has been demonstrated recently by a different technic: in normal persons a sudden total obstruction of the airway is followed almost instantly by a plateau in the intrapleural pressure; in patients with localized emphysema or partial bronchial obstruction, a redistribution of intrapulmonary gas occurs after airway interruption, and the intrapleural pressure continues to decrease for some time.[99,200] Results of local collection of alveolar air by endobronchial catheterization[263,264] and intrapulmonary mixing studies of the two lungs separately[57] have added support for this mechanism of defective distribution. Demonstrable improvement of mixing and alveolar ventilation has been achieved in emphysema by pneumoperitoneum treatment,[79] in asthma by bronchodilators[16] and by resection of fibrotic, cavernous or emphysematous lung tissue.[77]

Respiratory Gas Exchange

Respiratory gas exchange pertains to the transfer of oxygen from its gas phase to the blood in the pulmonary capillaries and to transport of carbon dioxide in the opposite direction. Analysis of the arterial-blood gas composition is required to assess respiratory function; peripheral venous blood is unsatisfactory because its gas content depends to a great extent on local metabolism and rate of blood flow through the tissues.

Arterial Oxygen Content and Percentage Saturation

The diagnosis of hypoxemia, or abnormally low oxygen saturation of the arterial blood, is often made clinically on the basis of cyanosis although it has been known for many years that blueness of the skin can occur without concomitant arterial hypoxemia and that severe tissue anoxia may not be accompanied by clinically evident skin discoloration.[265] It is accepted that cyanosis does not become evident until the arterial oxygen saturation has decreased to 80 per cent. During recent observations by 120 physicians concerning the skin color of patients with known and controlled arterial oxygen saturations, only 49 per cent identified cyanosis when oxygen saturations were between 81 and 85 per cent, and some did not rec-

ognize it at 71 to 75 per cent.[266] Most observers were inconsistent in their judgment of cyanosis in different patients or the same patients at different times. It should be apparent that determination of the arterial blood oxygenation in chronic respiratory disease is as important as determination of blood urea in kidney disease.[8,267] In the majority of cyanotic patients pulmonary function is not at fault: in congestive cardiac failure cyanosis must be attributed to the very low venous oxygen saturation, and in congenital heart diseases, cyanosis due to venous admixture is aggravated by polycythemia.

The oxygen *content* of the blood is most reliably determined by vacuum extraction of the gas and manometric analysis, according to Van Slyke and Neill.[268] The technic has remained unchanged, and the sources of error and normal range of values have been amply discussed.[2,3,268,269] The arterial blood normally contains about 19 cc. of oxygen per 100 cc. of blood (volumes per cent) combined with hemoglobin, and 0.24 vol. per cent of oxygen is dissolved in the plasma. The *oxygen capacity* is obtained by analysis of the patient's blood after thorough exposure to room air, or it can be calculated from the hemoglobin content of the blood. The ratio of oxygen content to oxygen capacity leads to expressions of *percentage saturation*. Inactive hemoglobin is detected only by the second method based on hemoglobin content.[223] Because of failure to correct for technical errors, physically dissolved oxygen and inactive heme pigments, the normal oxygen saturation has been placed at 93 to 96 per cent. Recently, these figures have been revised upward to 97 or 98 per cent,[3,74,268,270-272] with only slightly lower values in the aged.[73,74] Exercise causes a rise of the blood oxygen capacity; serious errors are introduced if the resting capacity is used for calculation of percentage saturation during exercise. During room-air breathing, the peripheral arterial blood remains slightly unsaturated because the alveolar oxygen tension is too low for complete saturation of hemoglobin, because of normally occurring uneven ventilation and because of venous admixture from thebesian and bronchial veins. Contrary to the findings of some,[273] voluntary or carbon dioxide stimulated hyperventilation does lead to a measurable increase in oxygen saturation.[274,275]

Ear and channel oximetry permit continuous analysis of the arterial oxygen saturation. Some precision is sacrificed for the sake of convenience and the advantages of continuous registration and no necessity for arterial puncture. Oximeters have been used during anesthesia,[276,277] during clinical and physiologic studies,[120,278] to monitor the "steady state" of metabolic activity[279] and in abbreviated tests of pulmonary function.[118-120,280,281] Failure to realize fully the sources of error introduced by oximetry prevents proper interpretation of certain published studies. An extensive discussion of methods and problems of oximetry has been presented by Wood.[282]

Spectrophotometric determination of arterial oxygen saturation obviates certain technical difficulties of gasometric analysis. Simultaneous determination of oxyhemoglobin and reduced hemoglobin in undiluted blood without exposure to the atmosphere leads to an unequivocal statement of the percentage saturation (HbO_2 x 100/total pigment).[3,271] Results agree closely with gasometric methods[283] and are probably more accurate.[3]

Because the primary function of the lungs is arterialization of venous blood, a number of over-all pulmonary-function tests have been based on arterial oxygen saturation.[10,118-120,273,280,281,284] Unfortunately, the degree of arterial oxygen saturation bears no close relation either to pulmonary function or to disability. If excessive venous admixture occurs distally, severe hypoxemia may be found at the sampling site in spite of normal arterialization of the blood by normally functioning lungs. Pulmonary arteriovenous aneurysm, congenital cardiac lesions and acute atelectasis with perfusion without ventilation are most often responsible. Determination of the arterial oxygen saturation before and after breathing of pure oxygen is used to detect anatomic vascular shunts: if the saturation fails to increase with oxygen breathing, an intrapulmonary or extrapulmonary shunt mechanism is held responsible; a reduced arterial oxygen saturation due to pulmonary insufficiency is almost always improved by oxygen breathing. The possibility of surgical correction of congenital pulmonary and cardiovascular defects has called attention to this differentiation.

Arterial oxygen saturation is a very insensitive measure of effectiveness of alveolar ventilation, and severe pulmonary insufficiency and disability may exist without significant hypoxemia. In emphysema, in pulmonary fibrosis and even in far-advanced parenchymal tuberculosis, saturation is rarely decreased below 85 per cent; however, this relatively small unsaturation indicates that 40 per cent or more of blood in the pulmonary artery passes through the lungs unoxygenated. Among 68 patients with severe pulmonary emphysema a third had oxygen saturations over 92 per cent both at rest and during exercise.[76] Of 663 coal miners with respiratory complaints 83 were totally disabled; the mean oxygen saturation for that group was 90.5 per cent.[12] Incapacity due to bronchial asthma is not usually accompanied by arterial oxygen unsaturation,[16] and tuberculous patients with "compensatory emphysema" may be dyspneic at rest without demonstrable hypoxemia.[83] In these patients adequate oxygenation is maintained at the cost of an enormously increased work of breathing.[99,182,196,200] Loss of parenchymal lung tissue does not lead to unsaturation if the pulmonary circulation is effectively diverted: hypoxemia is uncommon after resection of an entire lung or even more tissue.[77,81,285]

According to the classification of hypoxemia made

by Comroe and Dripps[268] arterial unsaturation that is not due to venous-arterial shunts may be due to inadequate oxygenation of normal lungs, as with upper respiratory obstruction, respiratory muscular paralysis or insufficient oxygen in the inspired air; hypoxemia may be due to inadequate oxygenation of diseased lungs because of ventilatory, distributional or diffusional defects.[268] Causes and interrelations of cyanosis, hypoxia and hypoxemia have recently been reviewed.[267,268]

Arterial Oxygen Tension

The S shape of the oxyhemoglobin dissociation curve explains why arterial oxygen saturation does not define precisely the state of oxygenation of the blood. The relation of percentage saturation to *partial pressure* or *tension* exerted by oxygen in the blood is not linear. In the last, almost horizontal portion of the curve, a fall in oxygen tension from the normal 100 to 60 mm. of mercury causes only a slight fall in saturation from 98 to 92 per cent, provided that the blood pH does not change. In the region of fairly normal oxygen saturation, where oxygen tensions are above 60 mm. of mercury, the value cannot be read from the curve even if percentage saturation and pH are known. In the steep portion of the curve, where the relation between tension and saturation is almost linear, this reading can be made but is of little help clinically because only low tensions are involved. Direct determination of the arterial oxygen tension is therefore essential for a precise definition of blood oxygenation. More important, expression in terms of tension enables direct comparison of the partial pressure of gases in the arterial blood and in the alveolar air.

Until recently no methods were available for clinical determination of the blood oxygen tension. In the past decade two methods have been described that, although not yet suitable for routine use, have permitted extensive study of oxygen tension in normal man and in cardiopulmonary disease. The first, or bubble equilibration method, is a modification of the principle devised by Krogh.[286] A large volume of blood is equilibrated with a small air bubble. The subsequently determined partial pressures of gases in the bubble are considered to be identical with the partial pressures of gases in the blood. Modification of this method for clinical use requires limitation to relatively small quantities of blood (1 to 5 cc.) and gas analysis of bubbles of 0.01 cc. or less.[287-289] The method of Riley, Proemmel and Franke[289] has been modified and improved a number of times,[290,291] but most workers who have had experience with this technic will agree that it is difficult, requires constant supervision and is only moderately accurate.

Polarographic methods for determinations of oxygen tension are based on the fact that oxygen is reduced when a suitable voltage is applied to an electrode submerged in solution. The transfer of electrons during oxygen reduction is proportional to the oxygen tension. Tissue and plasma examination is not difficult,[292-294] but analysis of whole blood appears to present great problems.[295] In Europe commercial apparatus for polarography of whole blood has become available and has been used clinically with good results.[296]

Arterial-Alveolar Oxygen Difference

The relation of arterial to alveolar oxygen tension has been termed the *A-A gradient* and has acquired considerable clinical interest. Because direct samples of "alveolar air" and of pulmonary capillary blood cannot be obtained, the term "difference" is preferable to "gradient," which gives the false implication that the difference in oxygen tension is due solely to defective diffusion.

The problems of obtaining "alveolar air" have been discussed. Continuous end-expiratory sampling[106-109] avoids interruption of normal breathing, but gas from underventilated alveoli is not adequately represented in such a sample. Newly developed methods and concepts have provided a partial solution to this problem, and it is now believed that a representative composition of "alveolar air" can be calculated from the inspired oxygen tension, the respiratory quotient and the arterial carbon dioxide tension, provided that a steady state exists.[297-301]

The oxygen pressure of the pulmonary capillary blood also cannot be obtained directly. Peripheral arterial blood must be resorted to for analysis. It has a lower oxygen tension than the blood leaving the pulmonary capillaries because of distal admixture of venous blood from the thebesian, anterior cardiac and bronchial veins. Extrapulmonary abnormal arteriovenous communications and intrapulmonary arteriovenous aneurysm may lead, by admixture, to an elevated alveolar-arterial difference in the presence of otherwise normal lungs. Pulmonary disease may also cause an "admixture" effect if certain parts of the lung are poorly ventilated but normally perfused with pulmonary arterial blood. In acute atelectasis, admixture of this kind may lead to very low arterial oxygen tension and readily visible cyanosis. All the factors that may be responsible for uneven pulmonary ventilation, including locally altered elastic structure and regional partial obstruction of bronchi and bronchioles, may be responsible for an elevated alveolar-arterial difference owing to admixture of mixed venous blood.

The second factor that contributes to the alveolar-arterial difference has been defined by Lilienthal and his associates[298] as: ". . . the sum of the resistances interposed by the tissue-fluid barrier which separates the alveolar air from the hemoglobin molecule: capillary endothelium, plasma, erythrocyte wall and intracellular fluid . . ." The term *pulmonary membrane* has been assigned to this total tissue-fluid barrier. Lilienthal et al.[298] have devised a method of sepa-

rating the portion of the difference due to the membrane component from that due to the venous admixture component. The separation is based on the fact that, because of the shape of the oxygen dissociation curve, the venous admixture component is the dominant factor in the alveolar-arterial difference during ambient air breathing at sea level whereas the membrane component is chiefly responsible for the difference during breathing of low oxygen tensions and at high altitude.

The finding of an elevated difference caused by increased resistance of the pulmonary membrane has led to the development of the concept of "*alveolar-capillary block.*"[302] This term has been suggested for a syndrome, often referred to as "pneumonosis" in the older literature,[303] that includes a variety of pathologic processes characterized histologically by alterations in the alveolar-capillary "membrane" and physiologically by an increased resistance of the pulmonary membrane to diffusion of oxygen. Pulmonary scleroderma, granulomatosis due to exposure to beryllium, sarcoidosis and pulmonary fibrosis of unknown etiology are the most important entities in which "alveolar-capillary block" is primarily responsible for hyperventilation, dyspnea and disability.[140,302,304-306] The magnitude of the alveolar-arterial difference before and after cortisone or ACTH therapy for various types of granulomatous diseases of the lungs has been reported[307-309]; the degree of clinical improvement is usually accompanied by a decrease in the alveolar-arterial difference. In cirrhosis of the liver[279] and in anemia[310] an increase in venous admixture can be shown. In mitral stenosis the total difference is increased,[311-315] but which factor predominates and the response to surgery are not as yet clear.

Riley et al.[299] have made a detailed analysis of the factors relating the composition of respired gases to arterial blood. The interdependence of ventilation and pulmonary blood flow has been termed the *ventilation-perfusion relation.*

Oxygen Diffusion Capacity

Marie Krogh's[316] thesis of oxygen transfer across the alveolar-capillary membrane by simple diffusion has received much support from these studies; although the most critical experiments have yet to be performed, the Bohr theory of specific activity of the lung has been discarded.

To determine the diffusing capacity for a gas, it is necessary to know the partial pressure of the gas on each side of the membrane and the rate of transfer across that membrane. The oxygen pressure in the alveolar air and the rate of oxygen consumption (rate of transfer) can be determined by direct measurement or calculation. The oxygen pressure in the pulmonary capillaries cannot be ascertained directly but can be calculated by the methods just described.[278,299] The technical requirements are extremely rigid if these calculations are to be valid. The portion of the total alveolar-arterial oxygen difference that is the result of membrane resistance divided by the oxygen consumption is the diffusion capacity for oxygen. A decrease in diffusion capacity has been reported in most cases in which an increased alveolar-arterial difference was due to primary pulmonary disease.

Carbon monoxide methods developed by several laboratories[317-321] offer promise of more extensive clinical application. Carbon monoxide has such great affinity for hemoglobin that, if inhaled, it exerts negligible "back pressure" in the pulmonary capillary blood.[316,317] The rate of carbon monoxide uptake and its alveolar concentration is determined by newly developed physical methods of analysis, and its tension in the pulmonary capillary blood can be ignored. The diffusion capacity for oxygen and carbon monoxide should bear a constant ratio of 0.8. Filley et al.[318] have reported a fair correlation between oxygen and carbon monoxide diffusion capacity in man.

Carbon Dioxide and pH

Determination of the arterial carbon dioxide tension has assumed increasing importance with the recognition that hypercapnia with severe respiratory acidosis may lead to mental changes and coma, without concurrent hypoxemia.

In contrast to that of oxygen the carbon dioxide tension can be read from line charts based on the Henderson–Hasselbalch equation if the carbon dioxide content and the pH of the blood are known.[232,322] The carbon dioxide tension can also be determined directly by the bubble equilibration technic.[289] The method to be preferred probably depends on the accuracy of the pH measurement, which has been determined with an accuracy of 0.02 pH units by colorimetric technics.[324] Increasingly precise, commercially available glass-electrode pH meters have been preferred recently.[3]

Also in contrast to that of oxygen, it is generally accepted that no alveolar-arterial tension difference exists for carbon dioxide.[298,316,325] A number of calculations, including the alveolar equation[297-301] and the Bohr[104] dead-space expression by use of carbon dioxide,[110] are based on this assumption that the arterial and the alveolar carbon dioxide tensions are the same.

With hyperventilation, hypercapnia is due to metabolic alkalosis whereas with underventilation it is accompanied by respiratory acidosis. In addition to carbon dioxide content the pH or carbon dioxide tension must be known if the diagnosis is in doubt.

The finding of severe respiratory acidosis during oxygen administration to patients with chronic pulmonary insufficiency has received much recent comment.[268,326-329] Chronic hypoxemia and hypercapnia due to pulmonary insufficiency lead to insensitivity of the respiratory center to the usual carbon dioxide

stimulation, and respiration reverts to the more primitive control by blood oxygen tension. If the partial pressure of oxygen in the inspired air is raised by therapy the stimulus to breathing is lost. The consequent severe underventilation results in greater hypercapnia, which may lead to mental changes, central-nervous-system depression, coma and death.

Underventilation resulting in hypercapnia without hypoxemia is being recognized as a serious problem during anesthesia, and both hypercapnia and hypocapnia may lead to disturbances of respiratory control and metabolism during artificial respiratory maneuvers of prolonged duration. These problems have been reviewed in this journal during recent months.[330,331] A nomogram for estimation of proper ventilation during anesthesia and artificial respiration[331] may prove of great value if simple instruments for ventilation measurements are available. In general, anesthesia machines and respirators are not equipped to monitor the most important variable — ventilation.

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MEDICAL INTELLIGENCE

INTESTINAL POLYPOSIS AND PIGMENTATION OF THE LIP*

Report of a Case

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THE strange association of intestinal polyposis and melanotic spots of the oral mucous membranes was unrecognized in the English and American literature as a syndrome of diagnostic significance until recently.

With their classic description in 1949, Jeghers and his co-workers[1] alerted the medical profession to the puzzling association of these two rare conditions. These authors exhaustively reviewed previous articles in the world literature. Subsequent reports through January, 1954, have been reviewed.[2] An additional case has been reported by Bruwer, Bargen and Kierland,[3] who suggested the eponym, Peutz–Jeghers syndrome, for the condition, since Peutz[4] made the original observation and Jeghers et al.[1] contributed a definitive description.

The complete syndrome is rare, only 33 cases having been described. The case reported below is not typical of the condition, for it does not fulfill the criteria so well defined by Jeghers and his associates. However, it is interesting because, in spite of many similarities, it differs significantly in several respects from previously described cases. Furthermore, the importance of a careful gastrointestinal study in patients with circumoral or oral pigmentation is considered worth re-emphasizing.

CASE REPORT

A 39-year-old housewife was admitted to the Greenbrier Clinic on April 22, 1954, for a general examination. She had no specific complaints. A very dark, brownish-black melanotic spot was noticed near the center of the vermillion surface of the lower lip. This was approximately 3 mm. in diameter and was not concealed by a generous application of lipstick. She was not sure when the spot appeared, but she was sure that it had been present for "several years." She was equally positive that it had developed during her adult life, probably in her twenties.

A gastrointestinal history was carefully obtained because of the presence of the unusual pigmentation. No symptoms positively related to the gastrointestinal tract were elicited. Specifically, there had been no rectal bleeding or change in bowel habits. For several years she had experienced an occasional, mild discomfort in the right lower quadrant lasting from a few minutes to 3 or 4 days. Seven months before admission she had experienced a moderately severe, constant, right-upper-quadrant pain that radiated to the infrascapular area. There was no accompanying nausea, vomiting or fever. She was told that she had had a gall-bladder attack. She had had no subsequent pain of this nature. Roentgenographic examination revealed a normally functioning gall bladder.

The other systems were asymptomatic except for some nonspecific pain in the lower back and the leg.

An appendectomy had been performed at the age of 13, and a hysterectomy for menorrhagia at the age of 37.

The family history was most significant (Fig. 1). All 4 maternal siblings had had carcinoma of the intestinal tract, probably of the colon. The mother had died at 52, 1 maternal uncle at 56, and a 2d maternal uncle at 61 years of age, all of this disease. A 3d maternal uncle had had a carcinoma of the colon resected at the age of 66 and was living and well approximately 2 years later. The patient was sure that none of these relatives had had any abnormal pigmentation. (However, as Jeghers and his associates[1] point out, even close relatives are frequently unaware of pigmentation of the oral mucosa.)

Physical examination did not reveal any abnormal findings except the melanotic spot on the lip described. No pigmentation of the oral mucosa, face or digits was found. Proctoscopic examination revealed several small polyps (3 or 4 mm.) in the rectum and lower sigmoid. Double-contrast barium-enema studies gave no definite evidence of polyps in the colon, although several small, suggestive ring shadows were seen. A stool was negative for occult blood.

The hemogram, blood chemical constituents, urinalysis, basal metabolic rate, electrocardiogram and x-ray films of the chest, sinuses and lumbosacral spine were all within normal limits.

X-ray examination of the stomach and small bowel was not done. So much time was spent in searching the colon for polyps that the radiologist considered it unwise to subject the patient to another long fluoroscopic examination at that time.

She was referred to Dr. Harry E. Bacon, of Philadelphia, for definitive treatment of the rectal and sigmoidal polyps. Sigmoidoscopic examination by Dr. Bacon "revealed 8 small mamillations and papillomas in the rectum." Under spinal anesthesia for removal of the polyps, 6 more were discovered, making a total of 14 adenomatous polyps in the rectum and sigmoid. These were fulgurated or excised. The pathological diagnosis of the excised polyps was "polypoid adenomas of the rectum." Dr. Bacon plans to re-examine the patient sigmoidoscopically and radiographically every 3 months for the next 3 years and every 6 months thereafter.

DISCUSSION

The two essential features of the syndrome described by Peutz and Jeghers are mucous-membrane pigmentation and intestinal polyposis. Both features were present in the case reported above, which differs significantly in some respects from the cases of the original authors.

All the patients described by Peutz[4] and all but 1 of those of Jeghers et al.[1] had some small melanotic spots about the facial orifices, primarily the mouth, in addition to the mucous-membrane pigmentation. Most of them had some digital pigmentation. These authors, however, did not consider the dermal pigmentation an essential part of the syndrome. Peutz[4] noted that the dermal spots tended to disappear but that the mucosal spots seemed to be permanent. Jeghers and his associates[1] stated that "the mucosal pattern is the *sine qua non* of the pigmentary part of the syndrome."

Multiple mucosal spots were present in all the cases in the literature. Examination revealed only one, which was very striking, in the case presented above. This raises an interesting question: How many mela-

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notic mucosal spots are necessary to fulfill the pigmentary criteria of the syndrome?

It could be logically questioned whether this is a simple case of multiple polyposis of the colon, with an unrelated, coincidental pigmentation of the lip. However, striking, brownish-black melanotic pigmentation of the vermillion surface of the lip is a rare occurrence. Physicians who examine hundreds of people a year have said that they cannot recall seeing a similar example of such pigmentation. Multiple polyposis of the colon, although not rare, is infrequent. The probability of the fortuitous, simultaneous occurrence of both conditions must be very small.

The pigmentation appeared early in life in the cases previously described. In 1 of the cases reported by Jeghers et al.[1] it was present at birth; in another a photograph at three months of age clearly revealed the telltale spots. The patient described above was sure that her spot had not appeared until she was in her twenties.

Patients with this syndrome are typically dark skinned and dark haired. The patient whose case is reported above had a very light complexion and light-brown hair.

Intestinal polyposis constitutes the symptomatic part of the syndrome.

In all the cases previously described, except 1,[5] polyposis of the small intestine has been a prominent finding. The majority of patients had as the presenting complaint symptoms characteristic of small-bowel intussusception, beginning typically in the second decade of life. The polyposis of the small intestine was usually found at laparotomy.

Although Peutz and Jeghers, McKusick and Katz considered small-bowel polyposis to be an essential feature of the syndrome, polyps were also found in the stomach, colon and rectum in most of their cases. Peutz[4] described a case of nasal polyposis and one of urinary-bladder polyposis. Thus, polyposis of most of the entodermal structures can participate in the syndrome.

The presence or absence of small-bowel polyposis has not yet been established in the patient described above, owing to practical considerations. Because of the well known propensity of rectal and colonic polyps to become malignant, and in the presence of the family history, it was considered wise to focus on the large bowel for the present.

Small-bowel adenomas are probably potentially malignant but certainly not to the same degree as those of the large bowel.[6] I hope later to have the opportunity of making an x-ray study of the patient's small intestine for academic as well as practical reasons. Until polyposis of this intestinal segment is proved, this case cannot be considered an example of the syndrome, in spite of the many similarities.

Practically, the management of asymptomatic polyposis of the small bowel presents a difficult problem. This essential segment of bowel cannot be removed in toto as the colon can, and it is virtually impossible to resect all the polyps locally. In my limited experience with asymptomatic multiple polyps of the small bowel (without pigmentation) outstanding bowel surgeons have thought it unwise to attack the condition surgically until symptoms intervened.

Jeghers and his associates[1] state, "Apparently the type of intestinal polyposis present in this condition becomes manifest early in life." In some cases polyposis has been discovered in infancy; in most it is first manifest in young adulthood.

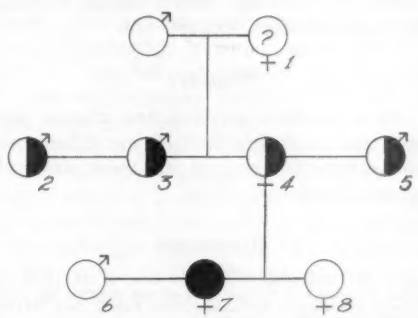

FIGURE 1. *Significant Genealogy of a Patient with Intestinal Polyposis and Pigmentation of the Lip.*

Grandmother (1) died of an abdominal cancer. A maternal uncle (2) died at the age of fifty-six of carcinoma of the bowel. Another maternal uncle (3) died at sixty-one of carcinoma of the bowel. The mother (4) died at the age of fifty-two of carcinoma of the bowel. Still another maternal uncle (5) had carcinoma of the bowel resected at the age of sixty-six. A brother (6) died at thirty-nine of an accident. The patient (7) was thirty-nine. A twin sister (8) was alive and well (not examined).

The present case also differs in this respect. The polyposis was still totally asymptomatic at the age of thirty-nine, two decades beyond the usual age of symptoms, and was discovered only because it was specifically searched for. One cannot, of course, know how long the polyposis had been present. However, because the polyps were of uniformly small size, they were probably of relatively recent origin.

The hereditary nature of this disease has been well established by Peutz[4] and by Jeghers et al.,[1] who believe it to be inherited as a simple mendelian dominant with a high degree of penetrance. Males and females both carry the factor, and both are equally affected with the disease. The genealogy of the patient discussed above suggests a similar hereditary pattern as far as the intestinal neoplasia is concerned (Fig 1).

It has been postulated[1] that a single pleiotropic gene is responsible for both characteristics of the syndrome, and this may well be the explanation. However, since there are no proved cases of the characteristic pigmentation without polyps,[1] and since polyposis without pigmentation with the same genetic

pattern has been observed much more frequently than the complete syndrome,[7] one can speculate on other possible mechanisms to explain the strange association of the two features. One wonders if the polyposis may represent the genetic feature of the syndrome and if there is possibly some subtle hormonal or nervous relation between the polyposis and pigmentation such as that postulated between cancer of the stomach and acanthosis nigricans or between the adrenal glands and dermal and mucosal pigmentation.

Whatever the explanation of the relation of the two characteristics, when one is observed the other should be searched for. Particularly, any unusual pigmentation about the mouth should stimulate a careful gastrointestinal examination.

Summary

A case of intestinal polyposis and unusual pigmentation of the lip is described. Some differences and similarities between this case and those previously reported are discussed.

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YOO-YOO'S DISEASE

An Often Encountered but Ill Defined Condition

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During a visit some time ago to a distant metropolis, I was asked to see a fifty-five-year-old man whose diagnosis had puzzled many of the specialists who had seen him. The problem was indeed complex and involved, an obscure bone thickening, cutaneous eruption, hypertension, splenomegaly with a mild anemia and a normal bone marrow. After much study without a definitive diagnosis, the patient had been referred to another medical center, where he again underwent an intensive investigation. The results confirmed those obtained previously and failed to uncover any substantial recommendations, except for one item.

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After I had seen and examined the patient, my host, the attending physician, asked me, "Have you ever heard of Yoo-Yoo's disease?" To confirm what I had heard, I asked him to spell it and then, a little abashed at my ignorance, resignedly admitted that I had never heard of such a condition and was not aware that the characteristics of the disease this patient presented fitted any single diagnosis. Thereupon, my host and the group of physicians who accompanied us uniformly uttered a sigh of relief mixed with frustration. My host related that he had obtained a complete duplicate record of the patient's stay at the most recent medical center to which he had been referred, and that, although the letter from the consultant had made no mention of it on the discharge summary note, a diagnosis of Yoo-Yoo's disease had been made. My host had no previous knowledge of this condition, nor had he been able to find anyone who was aware of a condition by this name. He had consulted texts, encyclopedias, the *Quarterly Cumulative Index Medicus* and similar sources and had been unable to obtain even the slightest hint of this disease or the eponym.

After assuring myself that I was not being made the victim of a medical practical joke and that the attending physicians were most sincere, I asked to see the record. Sure enough, there at the bottom of a long list of diagnostic possibilities was this ephemeral term, "Yoo-Yoo." The signature on the report was apparently that of an intern or resident and had been accorded the casual in-attention. I promised to resolve this impasse to the best of my ability, and on my return to the university I applied myself with great diligence to explain the mystery, which had by now become a *cause célèbre*.

A search of the usually reliable reference sources was fruitless. I began asking the esteemed encyclopedic specialists of the faculty who seemingly are always ready with complete details of the latest, the most unusual, as well as the long-forgotten medical oddities. The net result was a complete blank. In desperation I announced my desire for information concerning Yoo-Yoo's disease on ward rounds, only to be met with much quizzical scratching of head, resigned shrug of shoulder and a characteristic nonrevealing blank stare. I was about to admit defeat when the entire problem was solved in a moment of inspiration by the youngest resident. He triumphantly produced the second edition of *Standard Nomenclature of Diseases*,† and there on page xii was "y00 - y00. . . complete ignorance of the nature of a disease both as to location and cause." I might add that the senior faculty accepted this defeat with proper obeisance and with a new respect for the standard nomenclature. No increased desire for coding of charts resulted, however.

†*Standard Nomenclature of Diseases and Operations.* Edited by R. J. Plunkett and A. C. Hayden. Fourth edition. 1034 pp. Philadelphia: Blakiston, 1952. P. xii.

In the past few years this term has been applied to a complex clinical condition until a definitive diagnosis can be made. The term Yoo-Yoo's disease, therefore, is highly recommended as a temporary and expressive label that often flavors medicine with the frosting of challenge that humbles the esteemed and rewards the tyro.

1500 East Duarte Road

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41071

PRESENTATION OF CASE

First admission. A sixty-one-year-old man was admitted to the hospital because of a swelling of the left side of the neck.

Two years before admission, a brown mole was removed from the back of the patient's neck by electrodesiccation. It recurred shortly after excision and slowly grew to 2.5 by 2.0 cm. in size. Five weeks before admission a firm, nontender lump in the left side of the neck was biopsied and reported as an anaplastic type of carcinoma. The patient was referred to this hospital for definitive therapy.

A review of the systems revealed occasional precordial pain with exercise, mild dyspnea with exertion, and orthopnea requiring two pillows for relief. The remainder of the past history was noncontributory.

Physical examination showed numerous large, nonfixed, firm, slightly tender lymph nodes in the left posterior triangle of the neck. Between the upper portions of the scapulas, just to the left of the midline, was a pigmented lesion measuring 2.5 by 2.0 cm. The chest was normal. The heart was slightly enlarged, and Grade 1 systolic and diastolic murmurs were heard in the fourth intercostal space along the left sternal border. An examination of the ears, nose and throat revealed chronic laryngitis and no evidence of nasopharyngeal disease.

The temperature was 99.8°F., the pulse 92, and the respirations 24. The blood pressure was 210 systolic, 80 diastolic.

Urinalysis was negative. The hemoglobin was 15.5 gm. per 100 cc., and the white-cell count 6800. The nonprotein nitrogen was 32 mg., and the total protein 7.8 gm. per 100 cc. A blood Hinton test was positive. An electrocardiogram was interpreted as consistent with hypertensive heart disease. An x-ray film of the chest showed enlargement of the left ventricle; the lungs were clear. Films of the paranasal sinus were clear and gave no evidence of bone destruction. A metastatic x-ray series revealed several small, ovoid, punched-out areas in the skull and a similar area in the upper portion of the left ilium near the sacroiliac joint.

On the third hospital day, the pigmented lesion was excised with a radical neck, axillary and trapezius-muscle resection in continuity. The pathological report was malignant melanoma, with metastases to eight of twenty-eight lymph nodes. The postoperative course was unremarkable, and the patient was discharged on the eighteenth hospital day.

Final admission (two and a half months later). During a clinic visit a month after discharge, a 3-cm. mass below the left mastoid process was noted for the first time. On a return visit a month later, the patient first complained of weakness in the right lower extremity. On the day before admission a sudden severe pain on motion in the region of the right hip developed. He had gained 8 pounds in weight after the operation and had been feeling generally well.

Physical examination revealed a 3-cm. soft, deeply fixed mass at the upper end of the radical neck scar. Bilateral basilar rales were heard in the chest. The heart was enlarged, extending to the anterior axillary line, and a Grade 2 aortic systolic murmur was audible. The liver was not palpable, but there was a questionable mass in the left upper quadrant, suggesting splenomegaly. Deep local tenderness was found to the right of the trochanter. The right knee jerk was more active than the left.

The temperature was 98.8°F., the pulse 84, and the respirations 20.

Urinalysis showed + tests for sugar and acetone. The blood hemoglobin was 15.0 gm. per 100 cc., and the white-cell count 24,300. A film of the right hip demonstrated a complete, comminuted, partially impacted fracture through the neck of the right femur, with no significant displacement.

A medical resident on the day of admission elicited no cardiac symptoms, except for a history of many years of orthopnea relieved by two pillows and five years of gradually increasing dyspnea on exertion. The blood pressure was 140 systolic, 70 to 40 diastolic, in the left arm and 170 systolic, 70 to 50 diastolic,

in the right arm. Cardiomegaly (the border extending to the anterior axillary line), with sounds of good quality, was noted. A Grade 2 harsh apical systolic murmur was heard; a Grade 3 harsh aortic systolic murmur was transmitted to the neck; and a Grade 3 decrescendo diastolic murmur was best heard along the left sternal border in the third interspace. Marked pulsations of the neck arteries and capillary pulsations were observed. The patient was digitalized on the second hospital day.

On the fourth hospital day a nail and plate were applied to the right femur. The postoperative course was initially uneventful.

On the twelfth postoperative day, the temperature spiked to 101°F. A red, sore throat was noted, but the chest was clear. The operative wound appeared to be healing well. Streptomycin and penicillin therapy were begun. The patient's condition deteriorated rapidly during the next three days. The temperature, after an initial drop, rose to 105°F. The cardiac rhythm was irregular, with an apical rate of 200. The radial pulse was 130. Some coarse rales were heard at the left-lung base. The respirations were 36. There was a suggestion of early clubbing. Urinalysis showed a ++ test for albumin, a green test for sugar and 4 red cells, 6 white cells, many granular and a few hyaline casts per high-power field in the sediment. An electrocardiogram revealed atrial fibrillation with a ventricular rate of 200 and hypertrophy of the left ventricle. Therapy consisted of intravenous administration of Cedilanid, 0.8 mg. The cardiac rhythm became sporadically regular. The patient was restless in bed. His face had a sardonic expression, and he uttered inaudible words periodically and occasionally bit his lips. The eyes roved from side to side; both pupils were small and reacted sluggishly to light. The neck markedly resisted forward flexion. The tendon reflexes were active in both arms and legs. Tone was increased in both arms. Ankle clonus was present and more active on the left than the right. The plantar responses were flexor bilaterally.

Lumbar puncture revealed an initial cerebrospinal-fluid pressure equivalent to 160 mm. of water. The fluid had a ground-glass appearance and contained 2200 white cells per cubic millimeter, 99 per cent of which were neutrophils; the protein was 45 mg., and the sugar 87 mg. (the blood sugar was 200 mg.) per 100 cc. Culture of the urine was negative. An electrocardiogram, taken while the cardiac rhythm was regular, revealed a recent anterior myocardial infarction, digitalis effect and hypertrophy of the left ventricle. Tetracycline was added to the other antibiotic therapy.

On the next day, the seventeenth postoperative day, the cerebrospinal-fluid culture and a previous blood culture yielded a heavy growth of *Staphylococcus aureus*. Penicillin and streptomycin were discontinued, and erythromycin was added to the tetracycline. Later in the day scattered petechial lesions appeared over the body; one of these was 1.5 cm. in diameter over the buttock and was partly vesiculated. A throat culture gave an abundant growth of beta-hemolytic streptococci.

At bronchoscopy on the eighteenth postoperative day a large amount of inspissated secretion was removed from the hypopharynx. The trachea and right bronchial tree were normal. Thick secretions were present in the left main-stem bronchus. Beyond this, 6 cm. from the carina, a yellow-white mass was bulging into the bronchial lumen from the mediastinal aspect. The left bronchial lumen could be seen laterally as a crescentic slit through which the bronchoscope could not be passed. The temperature was 102°F. on this day; the hemoglobin was 14.9 gm. per 100 cc., and the white-cell count 12,500.

A thorough re-evaluation of the patient's status revealed a grimacing, stuporous man, who responded to painful stimuli. Bullous erythematous papules were noted on the right buttock. The neck was still stiff to forward flexion. The eyes were roving; the pupils were 2 mm. in diameter and fixed. The posterior pharynx was red, but no exudate was found. Decreased resonance was apparent at the base of the right lung, and crackling inspiratory rales were heard at both lung bases. The heart was enlarged, the border extending 2 cm. to the left of the midclavicular line; the position of maximal impulse was in the fifth left intercostal space 12 cm. from the midsternal line. The pulmonic second sound was greater than the aortic. A systolic thrill was felt in the neck on the right. A harsh medium-pitched systolic murmur in the aortic area was transmitted to the neck. A blowing, high-pitched decrescendo diastolic murmur was heard in the right and left second intercostal spaces and was transmitted down the left sternal border. A medium-pitched systolic murmur at the apex was not well transmitted. The abdomen revealed only hypoactive bowel sounds. The deep tendon reflexes were slightly increased on the right side. A slight droop of the left corner of the mouth was noted. Bilateral ankle clonus was more readily sustained on the left side. The left plantar response was down; the right was equivocal. Superficial reflexes were hypoactive.

On the nineteenth postoperative day, the temperature was 104°F., and the respiratory rate 45. Chloramphenicol was added to the other antibiotic therapy. On the twentieth postoperative day, the patient's respirations, which had been rapid, suddenly ceased.

Differential Diagnosis

Dr. Mark D. Altschule*: There are a few points I should like to have clarified. The note was made that a mass suggestive of splenomegaly was felt in the left upper quadrant; I wonder if the roentgenologist would tell us whether that was really the spleen or whether it was a retroperitoneal mass—

*Director of internal medicine, McLean Hospital.

such as a metastatic lesion in the adrenal gland, kidney or pancreas.

DR. JOHN F. GIBBONS: I hope we have an abdominal film. Meanwhile, I shall show you the other films.

DR. ALTSCHULE: You cannot change my mind; I have made it up on the basis of the clinical evidence.

DR. GIBBONS: These films show an enlargement of the heart, apparently primarily of the left ventricle. I do not see any abnormally aerated lung or mediastinal masses. The bones of the thoracic cage appear intact. In the skull there are small lytic areas scattered throughout the vertex, which were thought to represent metastatic neoplastic disease. In the pelvis there is an area of destruction of the upper corner of the left ilium. I do not see any other area except this part of the innominate bone, which looks as though it may be destroyed. When the patient was admitted the second time, he had a fracture of the right femoral neck that apparently was a pathologic fracture because there was evidence of bone destruction on the proximal side of the fracture line and the fracture was comminuted and impacted. I am sorry that I do not have a film of the abdomen.

DR. ALTSCHULE: Are there any later chest films that might show metastases?

DR. GIBBONS: No.

DR. ALTSCHULE: This patient had at least two diseases and possibly three or four. One of the diseases, of course, is metastatic neoplasm. It is interesting that the biopsy from the lump in the neck was called anaplastic carcinoma; that section was probably taken from an unpigmented area of the metastatic melanosarcoma, a highly malignant lesion. There was roentgenologic evidence of metastases to the skull. From the clinical history alone I could have guessed that the fracture of the hip was a pathologic fracture; the circumstances and the symptoms at the time all suggest pathologic fracture, but it is helpful to have the x-ray confirmation. In addition it is possible that metastases occurred more widely because this is a highly malignant type of neoplasm; the finding of a mass in the left upper quadrant might indicate metastases to the kidneys, tail of the pancreas or the adrenal gland, the last of which can present anteriorly sometimes. I think that is enough discussion of the neoplastic disease, which we agree the patient had.

The second disease is heart disease; that may have been several varieties together. When first seen he had hypertension, with a wide pulse pressure. A wide pulse pressure in itself is not diagnostic. A number of patients with hypertension have it; it is said to be associated with sclerosis mainly of the aorta, with relatively little in the smaller arteries, but that does not always prove to be true. Does the wide pulse pressure indicate disease of the aortic valve? Fairly early in the course he had systolic and diastolic murmurs, along the left border of the sternum, but they were quite low down in the fourth intercostal space. It is all right to hear an aortic diastolic murmur that low, but we should like to hear an aortic systolic murmur higher than that. However, the examination was apparently done on the Surgical Service. It would be helpful at this point to have some note about the presence or absence of capillary pulsation,— Duroziez's sign and pistol-shot sounds over the femoral arteries, — but I suppose those signs are out of fashion in this day of laboratory medicine. However, he did have a positive blood Hinton test when he was first seen so it is probable that he had syphilitic heart disease; on the other hand it is not proved because of the absence of definite evidence of the peripheral manifestations of aortic regurgitation. Another thing to remember is that sometimes patent ductus arteriosus causes the peripheral manifestations of aortic regurgitation. In view of the aberrant location of this murmur, which is wrong for both aortic valvular disease and patent ductus arteriosus, I suppose I ought to include both in my consideration. There is no note about whether this murmur was continuous or machinelike. Therefore, at least early in the course, there was no definite indication that he had either hypertensive or syphilitic heart disease with aortic regurgitation. Certainly, the x-ray films gave no evidence of dilatation of the arch of the aorta but that does not rule out syphilitic heart disease. The initial history of occasional precordial pain with exercise, mild exertional dyspnea, and orthopnea relieved by two pillows is consistent with hypertensive heart disease or at least with hypertensive and coronary-artery disease; on the other hand it is also consistent with aortic valvular disease. Narrowing of the ostia of the coronary arteries may give rise to anginal pain even when the arteries themselves are not involved in the disease. I am sure that he had heart disease before he came in to die, but I am not sure whether it was hypertensive or syphilitic heart disease; about 2 per cent of patients with hypertensive heart disease have diastolic murmurs. However, these murmurs are soft and usually higher up than the murmur described here.

Fifteen days after the operation on the femur he had rales in the chest on both sides. At that time no mention was made of diastolic murmurs. I do not know what to make of that; perhaps a different observer examined him. At any rate he did have rales. Did these rales indicate that the heart was beginning to fail or that metastases had invaded the lungs? There is still no definite information. The questionable mass in the left upper quadrant suggesting splenomegaly was also noted at that time.

The white-cell count on admission was 24,000. At that time, shortly after the fracture, he was not terribly sick and had no fever. I do not think a white-cell count of 24,000 can be explained on the basis of the metastases and fracture unless the metastases had given rise to infection in the lungs or some such con-

dition. The blood pressure was 140 systolic, 70 to 40 diastolic, in the left arm and 170 systolic, 70 to 50 diastolic, in the right arm. I take it that on the previous admission the examination was made on only one arm — the one that happened to be nearest the house officer. In view of the positive serologic test I am somewhat disappointed that the examination of both arms was not made earlier. At this time the aortic systolic and diastolic murmurs were heard in the third intercostal space, and capillary pulsations were observed. There was, therefore, good evidence of aortic regurgitation.

On the twelfth postoperative day, when the temperature rose markedly, the urine began to show all sorts of abnormalities — albumin, casts and so on. Central-nervous-system signs, which undoubtedly were associated with septicemia, developed, and, indeed, *Staph. aureus* was demonstrated by blood culture. The *Staph. aureus* was probably resistant to penicillin, and perhaps he acquired it on the occasion of the first admission to the hospital; hospitals have all sorts of interesting varieties of resistant staphylococci, which some patients carry home with them. There was also a suggestion of possible early clubbing. I wonder whether that observation was made after those treating the patient knew about the septicemia. Atrial fibrillation developed; arrhythmia is not uncommon in elderly men with infections and fever. The blood, stool and spinal-fluid cultures were all positive for staphylococcus. He therefore had a disseminated disease caused by septicemia or associated with it; he had signs of aortic regurgitation; he had petechiae, and he may have had a large spleen. It is evident that the picture is that of endocarditis. The organism was resistant to antibiotics, and he did not do well. We now have two diagnoses: bacterial endocarditis and metastatic malignant melanoma.

What did the endocarditis implant itself on? The most common varieties of heart disease that lead to endocarditis are congenital and rheumatic. He had no evidence of rheumatic heart disease, but he may have had it anyway, for he had aortic regurgitation. Syphilitic heart disease is only rarely the site of an engrafted bacterial endocarditis. Finally, endocarditis can become engrafted on a perfectly normal heart valve. I cannot say with any degree of assurance which it was.

Through the inevitable and more or less mandatory application of Leibniz's law I am forced to make the diagnoses of syphilitic heart disease, aortic regurgitation and superimposed bacterial endocarditis, the last explaining the blood, spinal-fluid and positive gastrointestinal cultures. The electrocardiographic evidence of the anterior myocardial infarction is also consistent with bacterial endocarditis of the aortic valve because thrombi can be carried into the coronary arteries from such a site. I should also predict that he had multiple abscesses in the various parts of the brain, the kidneys and undoubtedly elsewhere. The large mass in the lung seen by bronchoscopy, I think, was probably a metastasis.

DR. BENJAMIN CASTLEMAN: Are there any other suggestions?

DR. EARLE M. CHAPMAN: I am not familiar with Leibniz's law.

DR. ALTSCHULE: Leibniz was a well known German philosopher and mathematician; his law says that whatever seems reasonable is right.

DR. CHAPMAN: Other conditions seem reasonable to me. In this hospital and in others it has been pointed out that fat embolization to the lungs occurs after fracture. When this man returned he had a fracture and seemingly was in shock. I wonder if we might encounter fat emboli here. Would you consider that?

DR. ALTSCHULE: I should have added that to the possibilities.

DR. CHAPMAN: The other fact that worries me is that digitalis did not seem to help this man.

DR. FREDERIC C. GOETZ: It helped him a great deal, Dr. Chapman.

DR. CHAPMAN: Penicillin was given to this man, who probably had syphilis. His condition deteriorated rapidly during the next three days. Could that have been interpreted in any way as a Herxheimer reaction? We forget about the Herxheimer reaction these days.

DR. ALTSCHULE: I certainly forgot about it.

DR. CHAPMAN: Does the Herxheimer reaction occur after penicillin? We used to see it after the arsenic treatments were started.

DR. EVAN CALKINS: I think a febrile Herxheimer reaction is almost invariable, occurring two or three days after penicillin therapy, but it is very seldom accompanied by a change in the cardiovascular status.

DR. CASTLEMAN: Perhaps Dr. Chapman was instructing the fourth-year students because their diagnoses included syphilitic aortitis, with the Herxheimer reaction.

DR. GOETZ: One aspect of the case was perhaps not sufficiently dramatized in the protocol: on the service the signs of aortic regurgitation seemed to become more and more striking. The loudness of the diastolic murmur increased in the last seventy-two hours of the patient's life.

DR. ALTSCHULE: The other changes in the murmur seemed to be changes in location — it went from the fourth, to the third and finally to the second intercostal space. I assume that the observers were different rather than that there was a shift in the murmur.

DR. CASTLEMAN: What was the change in the murmur? Was there a continuous change in the murmur, or did it change only once?

DR. GOETZ: When I first saw the patient, during a bout of tachycardia, the heart rate was so rapid that the murmurs were definitely less impressive than when Dr. Jan Koch-Weser, the medical resident in the emergency ward, first described them. When the

heart rate slowed with digitalis the murmurs of aortic regurgitation seemed quite clear, what I should designate as Grade 3. In the subsequent seventy-two hours it became at least Grade 5, and the carotid pulsations were obvious from across the room, which they had not been previously. We suspected something new.

DR. ALTSCHULE: Was the mass that was felt the spleen?

DR. GOETZ: I cannot say that I actually felt the spleen.

CLINICAL DIAGNOSES

Meningitis due to *Staph. aureus.*
Septicemia, *Staph. aureus.*
Acute bacterial endocarditis.
Metastatic malignant melanoma.

DR. MARK D. ALTSCHULE'S DIAGNOSES

Syphilitic heart disease, with aortic regurgitation and superimposed bacterial endocarditis *(Staph. aureus).*
Myocardial infarction.
Abscesses in brain, kidneys and elsewhere.
Metastatic malignant melanoma, to lung and bone.

ANATOMICAL DIAGNOSES

Acute bacterial endocarditis, with perforation of right posterior aortic cusp and adjacent interventricular septum, with septic infarcts of heart, liver, spleen, kidneys and brain (Staph. aureus).
Syphilitic aortitis and valvulitis.
Malignant melanoma of skin with metastases to pleura, lung and (cervical lymph nodes).

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy we found a number of the conditions predicted by Dr. Altschule. The heart was enlarged and dilated (Fig. 1). The trabeculae carneae were somewhat flattened, and below the aortic valve there was a small, grayish, cusplike focus of endocardial fibrosis, which we see only in long-standing aortic regurgitation (Fig. 1—black arrow). Associated with that was a classic syphilitic aortitis. The aorta was very white and scarred and was covered with arteriosclerotic plaques in the ascending portion. There was no definite evidence of separation of the cusps at the commissures that one likes to see with a syphilitic aortic regurgitation, although the cusps were somewhat taut and the ring was certainly dilated, so that may account for the aortic regurgitation. There was an acute bacterial endocarditis involving all aortic cusps, with the perforation of one cusp. The endocarditis had sufficiently penetrated the myocardium beneath the perforated aortic valve to produce a septal defect. This could well account for the change in murmurs. On microscopical examination there was considerable destruction of the elastica of the aorta, indicating a true syphilitic aortitis.

The vessels of the kidneys contained septic emboli packed full of organisms producing numerous septic infarcts and well account for the recent urinary findings. The spleen was completely necrotic but not enlarged. We rarely see infarcts of the liver because it has such a good circulation, but one of the occasions on which we do is in bacterial endocarditis. This was true in this case. The fracture site that had been nailed was the greatest culture medium for staphylococci, outside the valve itself.

FIGURE 1.

DR. ALTSCHULE: Was there a mass in the left upper quadrant?

DR. CASTLEMAN: No; there was no mass in the left upper quadrant and no mass in the mediastinum.

A PHYSICIAN: Fat emboli?

DR. CASTLEMAN: We saw no fat emboli.

There was very little of the malignant melanoma in the body. There was, of course, the local recurrent nodule and a couple of nodules on the pleura, but that was all the tumor we were able to find. When the femur was explored, a great deal of pus was found. We took two blocks but neither of those showed any tumor. On going back to the record I get some indication that he had had pain in that hip for five years. That is just noted once in the record; whether that was true or not I do not know. The bacterial endocarditis, I believe, was quite acute. There was no evidence of organization. The temperature chart on the first ad-

mission was quite flat although the white-cell count was 24,300. I do not believe that the acute bacterial endocarditis had been present since admission.

DR. GOETZ: Do you base that opinion on the microscopical examination? On the gross specimen you thought it was of several months' standing.

DR. CASTLEMAN: Yes; microscopical study gave no evidence of any organization — just a very acute process. I wonder whether the endocarditis started to develop a week or so after the operation. I cannot be absolutely sure of that, and I certainly should not want to indict the nailing of the femur, but it is true that most of the staphylococci that we found were in that operative site. One could build up a case for that as the source of the staphylococcal septicemia and the endocarditis. Whether there was an underlying melanoma in that fracture site, we cannot decide on the evidence.

DR. GOETZ: Was there melanoma in the heart?

DR. CASTLEMAN: No; I believe the bacterial endocarditis was engrafted on a syphilitic aortitis, although previous heart disease is not necessary when there is an acute staphylococcal septicemia. We got pure cultures of staphylococci everywhere we took them.

DR. HOWARD ULFELDER: Were there metastases to the skull?

DR. CASTLEMAN: We did not find any.

DR. GIBBONS: The lesions seen on the x-ray films may have been unusually large vascular lakes. We have only one lateral view, and there is no way of telling.

DR. ULFELDER: Do you have an x-ray film of the hip on the first admission? That might tell us whether there was a tumor in it at that time.

DR. GIBBONS: There was no lesion in that femur at that time.

DR. CASTLEMAN: The changes in the brain will be described by Dr. Richardson.

DR. EDWARD P. RICHARDSON, JR.: Gross examination of the brain showed generalized thickening of the leptomeninges, and multiple scattered small pale and hemorrhagic infarcts in cortex and white matter. The left posterior cerebral artery, which was free of atherosclerosis, was occluded in its distal course by antemortem thrombus, and the area of occipital cortex supplied by this vessel was soft and necrotic. On microscopical examination there was no generalized meningitis, but there were an unusually large number of macrophages in the subarachnoid space. The cerebral lesions were characterized by recent necrosis, within which there were frequent accumulations of polymorphonuclear leukocytes and histiocytes, suggesting microscopic abscess formation. Many lesions of this type contained clumps of cocci. The thrombus in the left posterior cerebral artery contained many accumulations of bacteria and large numbers of neutrophils. There was necrosis of the artery wall on one side. There were no changes in the brain to suggest neurosyphilis, and no evidence of metastatic neoplasm. The findings could all be explained by multiple septic emboli.

CASE 41072

PRESENTATION OF CASE

A seventy-seven-year-old woman entered the hospital because of dysphagia.

Three months before admission she noted that food appeared to stop at the level of the suprasternal notch, and she regurgitated much of it. About a week later she spontaneously became able to swallow again. She subsequently had five more episodes of dysphagia varying from several hours to a week in duration. For a week before admission she again had dysphagia, but during this time she had periods in which she could swallow liquids fairly well.

Fifteen years previously a radical mastectomy on the right had been performed for adenocarcinoma of the breast with metastases to four out of eight lymph nodes. Twelve years later she was treated with radiation therapy to the right side of the neck because of pain in the arm and a mass at the base of the neck. This mass was not biopsied but disappeared with the radiotherapy. Two years before admission she was treated with 2000 r of x-rays and with diethylstilbestrol because of pain and weakness in the right arm. This treatment afforded some relief of pain but no return of motor function. A biopsy of a nodule in the right axilla at this time was said to show no neoplastic disease. The nodule decreased in size with x-ray therapy.

On physical examination the patient complained of pain in the right hand. There was paralysis and edema of the right arm and partial ankylosis of the right shoulder and right elbow at 90° flexion. The pharynx showed no abnormalities, and the swallowing reflex was present. There was a fullness of the left supraclavicular region. The mastectomy scar contained no nodules. There was + bilateral ankle edema.

Urinalysis revealed a + test for albumin and a sediment loaded with small granular and hyaline casts. The hemoglobin was 10 gm. per 100 cc. The serum calcium was 8.2 mg., the phosphorus 3 mg., and the phosphatase 2.4 units per 100 cc. Barium-swallow examination showed an inverted, cone-shaped constriction narrowing the lumen to a diameter of a few millimeters at the level of the aortic arch. There appeared to be no destruction of the mucosa in the region of the stricture. A small amount of barium flowed through the obstructed segment, outlining a normal-appearing esophagus below the stricture (Fig. 1). Films of the skull, spine, pelvis and femurs were normal.

An operation was performed on the fourth hospital day.

Differential Diagnosis

Dr. J. Gordon Scannell*: "She subsequently had five more episodes of dysphagia. . . ." We are not told whether these episodes occurred after she ate large pieces of meat or other solid food; perhaps the patient did not remember. It would be helpful to know.

Three years before admission radiation therapy was given to the right side of the neck because of pain in the arm and a mass at the base of the neck. This is probably a departure from principle. No matter how useful treatment without a diagnosis may be to the patient, it makes it very difficult for the discusser of the case in the Clinicopathological Conference.

Figure 1. *Spot Film From Barium-Swallow Examination. There is narrowing in the upper esophagus, with esophageal dilatation proximally. A filling defect above the constriction probably represents some retained food. There is a suggestion of extrinsic pressure anteriorly (arrows).*

It is obviously very important to see the x-ray films, for I am sure that they will be the most important single aid to making the diagnosis in this patient.

Dr. Joseph Hanelin: The films made at the time of hospitalization show a conical type of esophageal narrowing at the level of the aortic arch (Fig. 1). The narrowing is slightly asymmetrical in that, although it is smooth, there is some suggestion of pressure anteriorly on the esophagus at the point of maximal constriction. Just proximal to this area, there is a filling defect, which changes somewhat in size; I suspect, therefore, that there is food above the narrowing although I cannot exclude a protein material other than food.

*Assistant surgeon, Massachusetts General Hospital.

Dr. Scannell: Do you mean a tumor?

Dr. Hanelin: Yes. The lungs are clear except for some thickening of the pleura over the right apex. This may result from irradiation; neoplastic change at the apex could also cause this density. The right leaf of the diaphragm is elevated more than usual. This may be related to pulmonary fibrosis secondary to irradiation because no paralysis of the diaphragm is mentioned.

Dr. Scannell: Would you comment on the mediastinum? Is there any evidence of adenopathy?

Dr. Hanelin: No; I do not see evidence of adenopathy. Of course one wonders if what is happening to the esophagus results from adenopathy, but I cannot be certain of any such change.

Dr. Scannell: It seems to me that this problem resolves itself into whether or not the esophageal obstruction in this seventy-seven-year-old woman was benign or malignant, and, if malignant, whether it was primary or secondary. I shall first discuss the benign causes, most of which I think I can discard.

Did she have a benign stricture? I think this is an unlikely area for any stricture except that produced by the ingestion of a caustic or other agent, of which there was no history. Moreover, the esophagus was normal below the level of the stricture; it was not greatly shortened, with the stomach up in the chest. She may have had an ectopic gastric mucosa at this level, but in general that is in the lower end of the esophagus and is usually associated with a long-standing history of esophagitis. Although we occasionally see a stricture at this level, I am inclined to believe that this was not a benign stricture.

Could this have been spasm of the esophagus? Spasm of the esophagus beginning at the age of seventy-seven would be most unusual indeed. It would also be unusual for the spasm to be limited to this level. The fact that the symptoms came and went does not disturb me. I do not think that means spasm; as a matter of fact with spasm I should expect more pain. I believe the intermittency of the symptoms was probably related to the diet. I doubt if there was a web. The x-ray picture does not look like that of a web. The patient was anemic, it is true, but perhaps the anemia was on a nutritional basis. The question of benign extrinsic pressure comes up. Certainly, a large aortic aneurysm or enlarged left atrium can produce obstruction, which is usually not complete. Neither the aorta nor the atrium was large as far as I can make out, so I think that is very unlikely.

The thought just crossed my mind that since she had x-ray therapy to the chest, she may have had a stricture of the esophagus similar to the stricture of the bowel resulting from x-ray therapy in the pelvis. I have not heard of this. I think it is unlikely, and it is unlikely that such a stricture would produce this x-ray picture. I should expect to see ulcerations and a longer-standing, more gradual increase in symptoms so that I shall rule out that possibility.

The remaining benign cause of esophageal disease is a benign tumor of the esophageal wall. Such tumors are quite uncommon although Sweet, Soutter and Tejada Valenzuela* described a series of 22 patients from this hospital. The lesions usually do not present this appearance, and in spite of the x-ray pictures, they usually do not produce obstructive symptoms. Having disposed of the benign causes I shall turn to the malignant causes of esophageal obstruction.

The malignant lesion most likely to have been present if she had not had a previous mastectomy would be primary carcinoma of the esophagus. This usually produces a different x-ray picture from the conical narrowing described. However, the narrowing is not so perfectly smooth and conical as I had expected, but is somewhat eccentric, with a questionable mass, which Dr. Hanelin euphemistically called protein; therefore, this could possibly be carcinoma of the esophagus. The history, the age and even the symptoms of intermittent dysphagia of relatively short standing are also perfectly consistent with this diagnosis. Moreover, this is a common location for carcinoma; in fact the lesion is low enough to favor primary carcinoma rather than an involved lymph node in the hilus. The absence of a large mediastinal mass makes me think in terms of primary carcinoma of the esophagus.

Was this a manifestation of metastatic carcinoma from the breast? The time interval was long, — fourteen or fifteen years, — and yet that is not disturbing since we have all seen late bizarre manifestations of carcinoma of the breast. We know that this patient had a metastasizing tumor from the original pathological examination and from the clinical history of the masses, which responded both to x-ray and to hormonal therapy like a carcinoma of the breast. Furthermore, the anemia is perhaps evidence of disseminated disease, although no such disease was demonstrated. The mediastinum is a frequent site for late metastases from the breast; however, when metastases occur there is more likely to be evidence of interference with the bronchi as well as the esophagus. Would you not say, Dr. Hanelin, that the bronchi look normal?

DR. HANELIN: Yes.

DR. SCANNELL: It would be unlikely for a metastasis from carcinoma of the breast selectively to obstruct the esophagus, without affecting the bronchial tree. This, of course, raises the question, Could there have been extrinsic pressure on the esophagus by primary carcinoma from the bronchial tree itself or elsewhere? That is an occasional cause of esophageal obstruction. Primary carcinoma of the bronchus would be unusual in a woman of seventy-seven. Also, one would expect more in the way of pulmonary symptoms.

Finally, could this have been one of the lymphoma series? If it had been, I should have expected a greater degree of hilar adenopathy. Until I saw the x-ray films I favored metastasis from the breast, but I shall switch now to primary carcinoma of the esophagus for the following reasons: the x-ray picture is consistent with that, the lesion is lower than I had thought it would be, and there is no evidence of hilar adenopathy.

DR. ALLEN G. BRAILEY: Do you think a diverticulum should also be listed among the benign conditions?

DR. SCANNELL: I suppose it should; but it did not occur to me when I looked at the x-ray films. Traction diverticulum is the type that would be present at this level. I do not believe that very commonly causes dysphagia — certainly not at this level.

DR. BENJAMIN CASTLEMAN: Dr. Sweet, have you a comment?

DR. RICHARD H. SWEET: I think I would have said exactly what Dr. Scannell did. I would not have thought of diverticulum. I have seen a patient with obstruction of the esophagus in whom exploration showed pressure on the esophagus by lymph nodes actually involved by metastases from oat-cell carcinoma of the lung. As they did Dr. Scannell, the x-ray films have influenced me in favor of the diagnosis of primary carcinoma in the case under discussion. Symptoms, as he pointed out, are ordinarily intermittent with benign stricture, but the history should be very much longer than three months for that diagnosis.

DR. CASTLEMAN: The radiologists called this a benign stricture of the esophagus.

DR. HANELIN: I had not seen these films before today. Certainly, the findings are not typical of a primary esophageal carcinoma. Usually, such a lesion is not as smooth and regular as the tumor in this case. I should wonder very seriously about extrinsic pressure on the esophagus and secondary invasion from a metastasis in lymph nodes. I cannot completely rule out a primary lesion in the esophagus. This filling defect just before the stricture might well be an intrinsic tumor.

DR. CASTLEMAN: The operation was an esophagoscopy by Dr. B. Frame and Dr. Benedict.

DR. EDWARD B. BENEDICT: The esophagus showed an absolutely smooth, symmetrical narrowing, which we thought was a benign stenosis. We dilated it with bougies from size 10 through 26 inclusive, without difficulty.

DR. ROBERT S. PALMER: What do you think caused the dark appearance of the right apex? Do you think it was due to the x-ray treatment, or was it incidental?

DR. HANELIN: It may have been the result of radiation therapy or may have been tumor; I cannot be certain.

DR. BENEDICT: We know that radiation fibrosis can cause narrowing of the esophagus. I do think that spasm enters into the picture intermittently, with either carcinoma or benign stenosis. Certainly, they all have an element of spasm.

*Sweet, R. H., Soutter, L., and Tejada Valenzuela, C. Muscle wall tumors of esophagus. *J. Thoracic Surg.* 27:13-35, 1954.

DR. HANELIN: I gather from the record that no x-ray treatment was given directly to the mediastinum — just to the neck and axilla. I doubt if that portion was radiated at all.

CLINICAL DIAGNOSIS

Benign esophageal stricture.

DR. J. GORDON SCANNELL'S DIAGNOSIS

Primary carcinoma of esophagus.

ANATOMICAL DIAGNOSIS

Metastatic carcinoma to esophageal wall from carcinoma of breast, resected fifteen years previously.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Although the lesion at esophagoscopy appeared perfectly smooth and looked like a benign stricture a biopsy through that stricture was fortunately taken.

DR. BENEDICT: We always take a biopsy; I believe that is extremely important.

DR. CASTLEMAN: A good-sized biopsy specimen was removed — 6 by 3 by 2 mm. Deep in the muscle layer, not involving the mucosa, was a tiny collection of small, uniform, not very atypical epithelial cells that we called probably carcinoma, since we had not received any information about the patient. We were sure that they were epithelial cells, did not believe they were from a primary carcinoma of the esophagus, but could not rule out such a condition as an extension from a bronchial adenoma. With a definite history of carcinoma of the breast there is no question in my mind that it was metastasis — probably, an extension from metastatic involvement of a lymph node. It is unusual in that the bronchus was not involved. Usually, the first structure compromised by a late metastasis from a carcinoma of the breast to the mediastinum is a bronchus.

There is still an opportunity for groups using the Case Records as teaching exercises to subscribe for lantern slides to go along with the current cases. The cost for this service is $100 a year, as pointed out in the editorial in the February 3 issue of the *Journal*. Applications are to be sent to Dr. Benjamin Castleman at the Massachusetts General Hospital, Boston.

MASSACHUSETTS PHYSICIANS ART SOCIETY

35. *Percé Rock*

Oil Painting by

FRITZ B. TALBOT, M.D.

Formerly, Chief, Children's Medical Service
Massachusetts General Hospital

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MEETING OF THE COUNCIL

THE meeting of the Council of the Massachusetts Medical Society on February 2 was a test of endurance for the Society's representatives and an instance of unparalleled hardihood on the part of the loyal quorum that remained until the meeting adjourned at 4:08 p.m. Not only did this meeting illustrate the intelligent interest taken in the Society's affairs by a large majority of the councilors; it served as a shining example of the capacity of those same councilors to debate extemporaneously, eloquently and at length on almost any of the problems that confront organized medicine.

Most of the reports submitted to the Council were accepted and approved as routine matters; a half dozen were sufficiently controversial to require adequate ventilation before being settled one way or another. The matter of the use of the Society's stationery, or a facsimile thereof, in a high-pressure campaign put on by an agency approved by the Council to sell accident and health insurance to the fellows of the Society was variously considered. The Subcommittee on Accident and Health Insurance of the Committee on Public Relations had approved such use and was sustained by a majority of the councilors present over the objections of those who believed that it was improper.

The matter of House Bill 705, introduced into the General Court of Massachusetts for the purpose of setting up a new nurses approving authority, had been viewed with favor by the Committee on State Legislation. Despite affectionate and somewhat nostalgic allusions to Sarah Gamp and her philosophy of nursing, the bill was argued on its presumed merits in relation to the practice of medicine and the care of the patient. In rebuttal of the statement that the present plan does not function well, it was pointed out that the need is not so much for a new law as for the means properly to implement the present one. With expressions of the utmost regard and admiration for the nursing profession and its component members the Council nevertheless decided that it should not commit the Society to an approval of the bill in its present form, and referred it back to committee for further study.

The sagacious recommendation made by the Committee on Finance and the Treasurer, after consultation with the Department of Internal Revenue, that a charitable and educational fund be established as soon as possible as a repository for tax-susceptible income nearly foundered in a sea of eloquence and was towed back to port for repairs.

The recommendations of the Committee on By-Laws in regard to district-society membership, a matter introduced by Dr. Robert M. Holland, of Norfolk, were warmly but pleasantly debated. The fact that fellows of the Society are permitted under the *By-laws* to change their membership from the district in which

they reside, on approval of the Committee on Membership, has long been known to conflict with Article VII of the act incorporating the Society. The Committee therefore recommended changes in the *By-laws* to make them consistent with Article VII of the statutes. The advice of the Executive Committee that the matter be referred back to the Committee on By-Laws for consultation with the Committee on Membership was accepted by the Council.

The report of the Committee on Welfare Problems re-emphasized the unhappy relations that exist with the Commissioner of Public Welfare of the Commonwealth. The Commissioner's apparent fixed belief that the physician, at least, is not worthy of his hire seems to have been impossible to eradicate. It is encouraging that the president of the Society has found the Governor sympathetic and understanding and has accepted an appointment by His Excellency to the Advisory Board of the Department of Public Welfare.

The report of the Committee on Employment of the Handicapped, an important and controversial matter, was referred back to the Committee for further study.

President Tripp, the officers of the Society and the chairmen of the committees are to be congratulated on the able manner in which they conducted the affairs of the Society through a prolonged and involved session.

"AGAMMAGLOBULINEMIA"

Most physicians have encountered patients who, they have instinctively felt, had some deficiency in ability to cope with infections. Some of the factors that are known to alter the responses of the host to pathogenic or even, at times, to saprophytic organisms include local anatomic changes, such as obstruction to hollow viscera and diminished blood supply, changes in the reactivity of the tissues in such metabolic disturbances as scurvy, cortisone therapy and diabetes, and failure of the normal defense mechanisms, as in patients with neutropenia or under heavy anesthesia.

During the last few years specific deficiency of the gamma-globulin fraction of the plasma proteins has been added to this list of conditions in which susceptibility to infection is marked. The terms hypogammaglobulinemia and agammaglobulinemia have been used to designate low and undetectable levels of gamma globulin respectively, generally measured by the electrophoretic method of analysis. A lower than normal level of any specific blood protein or blood cell may be due to a diminished rate of formation or delivery to the circulating blood, to an increased rate of utilization, destruction or loss from the circulation or to a combination of these processes. Hence the mechanism of such an abnormality as agammaglobulinemia cannot be assumed to be due to a diminished rate of formation in any given case unless data on this or on the rate of disappearance of injected tracer doses can be obtained. Fortunately, with the availability of radioactive isotopes and purified protein fractions, this can be done quite readily on a research basis, providing valuable new insight into the pathogenesis of disturbances of specific plasma proteins.

Bruton, in 1952, described the first case of agammaglobulinemia in an eight-year-old boy, who from the age of three and a half years had had multiple attacks of pneumococcal infection, including ten with bacteremia, some of them due to the same pneumococcal type. Failure to develop circulating antibodies in response to the injection of a series of antigens led to the electrophoretic analysis of his plasma and recognition of the absence of gamma globulin. Since that time, approximately 30 similar cases have been observed in children in various clinics in the United States and abroad, particularly at the Children's Medical Center of Boston by Apt and his colleagues and at the University of Minnesota Hospitals in Minneapolis by Good.

It is quite clear that, in this group, the defect is genetically determined, with inheritance as a sex-linked recessive, analogous to that of hemophilia; all the children have been males, and, although some of their male siblings appear to have had the same disease, no female siblings with this condition have been observed. These children suffer from an early age with repeated severe infections with all the common pyogenic bacteria, with involvement of skin (pyoderma), conjunctivas, upper and lower respiratory tracts and meninges. Their defect is clearly due to inability to synthesize gamma-globulin antibodies and is associated with pathologic changes in all the lymphoid tissues as shown by Craig, characterized by an atrophic condition at post-mortem examination and by the failure of formation of secondary follicles or differentiation of plasma cells on antigenic stimulation. The half life of injected gamma globulin, according to Gitlin, is as long as or longer than normal, thus ruling out an abnormally rapid destruction or loss of gamma globulin as a cause of the deficiency.

It is of great biologic interest, as shown by Good, that these children demonstrate the normal "acute-phase" reactions and develop nonspecific tolerance to bacterial pyrogens, although they do not form antibodies. He has also reported successful homotransplantation of skin to 1 of these patients.

This condition should be suspected in any young male with unusually severe or recurrent infection, particularly if neutropenia is observed. If isohemagglutinins for appropriate blood groups (in children of Groups A, B and O) are absent from the serum or if the Schick test is positive after adequate immunization, this is presumptive evidence for the diagnosis, and the child should be studied by more accurate chemical methods. Early recognition of this condition is very important. Administration of gamma globulin (immune serum globulin) in doses of at least 0.1 gm. per kilogram of body weight (0.3 cc. per

pound) every four weeks is quite effective in the prevention of infection in these children, provided its use is begun before permanent damage (such as hydrocephalus secondary to meningitis or bronchiectasis secondary to pneumonia) has developed.

In contrast to this congenital or primary agammaglobulinemia, acquired or secondary agammaglobulinemia may develop at any age or in either sex. A striking case history written by a patient with this disease appeared in a recent issue of a popular magazine. Its causes are multiple. Some cases resemble congenital agammaglobulinemia, with similar pathologic findings in the lymphoid tissues, whereas in rare cases granulomatous or neoplastic changes in the lymphoid system appear to have replaced the normal tissue. These patients usually present the picture of recurrent pneumonia and severe bronchiectasis. Although in both congenital and acquired agammaglobulinemia gamma globulin cannot be detected by electrophoretic analysis, more delicate immunochemical methods applied by Gitlin have revealed small amounts in the blood of many of these patients with levels ranging from 0 to 100 mg. per 100 cc., but usually less than 30 mg. per 100 cc. in the congenital group.

Hypogammaglobulinemia occurs in a number of conditions. It is a physiologically normal finding in infants from one to six months of age. In the nephrotic syndrome the lowered gamma globulin level (about 200 mg. as compared with a normal value of 600 to 1200 mg. per 100 cc.) is presumably due mainly to rapid loss in the urine. Hypogammaglobulinemia has been observed in several types of congenital or familial dysproteinemia and as part of the syndrome of idiopathic hypoproteinemia. An unusual tendency to infection is generally not seen in these cases.

As more and more electrophoretic analyses are included in clinical laboratory routines, it is quite probable that an increasing number of disturbances of specific plasma proteins will be observed in various clinical situations. In the gamma globulins the related morphologic failure of plasma-cell differentiation in the lymph nodes, chemical deficiency of gamma globulins in the plasma, immunologic defect as manifested by failure of antibody formation and clinical picture of striking susceptibility to recurring pyogenic infections have been clearly delineated, although the specific genetically determined biochemical defect underlying these phenomena in congenital agammaglobulinemia remains to be elucidated.

DOUBLE STANDARD OF MEDICINE

THE Massachusetts Chiropractic Laymen's Association has, with the endorsement of Representative Charles H. Anthony (R), of Haverhill, petitioned the General Court for legislation to establish a board of registration of chiropractors. This year's petition to allow chiropractors to practice is printed as House Document No. 360, and in the course of legislative procedure will be given public hearing by the Committee on Public Health, made up of 4 Senators and 11 Representatives. Chairman of this Committee is Senator George J. Evans (R), of Wakefield. House chairman is Representative Frank B. Oliveira (D), of Fall River.

As in the past, the Massachusetts Medical Society will strongly oppose this legislation. As in the past, its representative will hear the chiropractors and their advocates argue that physicians oppose chiropractors because they fear that they will lose prestige and income; that chiropractic is *not* the practice of medicine; that the public should have "free choice" of "doctors"; and that chiropractors "cure" many patients with any number of diseases who were given up as hopeless by medical practitioners.

In House Document No. 360 chiropractic is defined as follows:

> . . . the science of locating, and removing by hand adjustment only, interference with the transmission or expression of nerve force in the human body, by the correction of misalignment of subluxations of the vertebral column. It excludes operative surgery, prescription or use of drugs or medicine, or the practice of obstetrics, except that the X-ray and analytical instruments may be used solely for the purposes of examinations . . .

The petition further requires that, to practice in Massachusetts, the chiropractor take a written examination, to "include the subjects of anatomy, neurology, symptomatology, physiology, X-ray, hygiene, sanitation, chemistry, pathology. . . ."

It is admittedly difficult for the Society to convince the general public and many of their elected representatives, in the face of undocumented, unscientific testimonials of chiropractic "cures," that the basic fundamental of chiropractic is completely unscientific. Despite his years of training and practice, a medical scientist is immediately suspected of selfish motives if he points out that the chiropractor's claim that misalignments in the spine cause cancer, poliomyelitis, heart trouble and so forth, owing to interference in the transmission of nerve force to and from the brain and the affected area in the body, is completely unscientific and that painstaking studies of the nervous system over the centuries never disclosed the system under which the chiropractor works.

The Society's spokesmen from time to time have been chided for pointing out that the chiropractor is poorly trained and uneducated in science. When chiropractors have compared their curriculum to that of Johns Hopkins University, the Society has stressed the fact that in medical education it is the caliber of the teachers that is the criterion, not the textbooks. A study of the faculties of chiropractic colleges in the United States revealed scarcely even a Bachelor or Master of Science degree among them. These are the faculty members who will prepare chiropractic students (who entered their halls just out of high school or with the equivalent of a high-school education) for written examinations in anatomy, neurology, physiology, pathology and the like.

The chiropractor argues that since chiropractic is not the practice of medicine, one should not interfere with the other. The Supreme Judicial Court of Massachusetts decided in 1915 that chiropractic is the practice of medicine. Yet the chiropractor will continue to argue that because he does not use insulin for treating diabetes or antibiotics for the management of acute infection, he is not practicing medicine.

Physicians bold enough to point out that a chiropractor who accepts patients and treats them for diseases is practicing medicine, although his treatment is "by hand adjustment only," have been charged with protecting the pocketbook of organized medicine.

The chiropractor's argument that the public should have "free choice" of "doctors" and the "right" to choose the "type" of treatment desired always sounds good. The Society's spokesmen have repeatedly emphasized, perhaps to some avail, the fact that a person's "right" often runs counter to common sense, and that laws to prevent many so-called "rights" have ancient ties. The arguments against the passage of House Document No. 360 will, of course, have to follow the same lines as in years past.

It is believed that the elected representatives will again reject the licensing of chiropractors in Massachusetts — despite the increasing pressure from the chiropractors and their adherents — if the following points are forcefully stressed: that the Massachusetts Medical Society was organized in 1781 for the expressed purpose of improving the standards of medical practice and medical education, and that the ethical physician will fight to maintain those hard-earned standards; that the medical profession is not worried over losing income and prestige to the chiropractor; that the medical profession opposes chiropractic purely and simply in the public interest; and that for the Legislature to license chiropractors would be tantamount to endorsing them and would result in a double standard of medicine in Massachusetts.

The Society argues that the best of scientific medical care and treatment offered by physicians educated and trained in the best of medical schools and hospitals should be maintained. There should be no lowering of standards and no double standard of medical practice in Massachusetts.

REGARDING MEDICAL NOMENCLATURE

SELDOM has a new disease been revealed so succinctly as has been done by Bierman, who treats elsewhere in this issue of the *Journal* of Yoo Yoo or, as he calls it, Yoo Yoo's disease. The eponym is of dubious value in naming this ill defined condition, for it implies an Oriental origin or distribution of the disease, or even an occupational condition, neither of which is one of its main characteristics. Then too, if the name were used routinely — and this is apart from any argument that can be made against the use of medical eponyms in general — the implication would be clear that it was Yoo Yoo himself who first described medical nosology, particularly of the signs, symptoms and location of lesions. Bierman makes it abundantly clear that Yoo Yoo had nothing to do with classification; he advances cogent reasons why, despite his own title, the simpler name seems preferable.

Perhaps the most interesting aspect of the case report lies in the "complex and involved . . . cutaneous eruption that accompanied the mild anemia and normal bone marrow." The diagnosis of erythema multiforme was never actually advanced, but it too may well be part of the cutaneous manifestation of this "complex clinical condition." In either event it is Bierman's signal contribution that he has dispelled ignorance concerning basic terminology and has emphasized once again correct grounds for the diagnosis of Yoo Yoo.

Members of the fourth-year classes in medical schools approved by the Council on Medical Education and Hospitals of the American Medical Association are reminded that the *Journal's* prize-essay competition closes on March 15.

Full details were published in the *Journal* of November 11, 1954.

Several complaints have been made by subscribers in the city that their copies of the first number of the present volume did not reach them. We hope that the addition of so many names to his list will serve as an excuse for some mistakes on the part of the carrier.

Boston M. & S. J., *Feb. 22, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BLOOMENTHAL — Herbert Myer Bloomenthal, M.D., of Brookline, died on January 23. He was in his forty-sixth year.

Dr. Bloomenthal received his degree from Middlesex University School of Medicine in 1937. He was a member of the staffs of the Evangeline Booth Memorial Hospital and Home and the Massachusetts Memorial Hospitals, the New England Gynecological and Obstetrical Society and the Association of Military Surgeons.

He is survived by his parents, widow, daughter, son, sister and two brothers.

BROWN — Ralph N. Brown, M.D., of Lynnfield, died on January 25. He was in his seventieth year.

Dr. Brown received his degree from Tufts College Medical School in 1912. He was a fellow of the American Medical Association and, formerly, president of the Malden Medical Society.

He is survived by his widow and two sons.

CLEVELAND — Harold F. Cleveland, M.D., of Springfield, died on January 19. He was in his sixty-sixth year.

Dr. Cleveland received his degree from Middlesex University School of Medicine in 1920.
He is survived by his widow.

CIVIL DEFENSE AGENCY

BASIC MEDICAL PROBLEMS ASSOCIATED WITH ATOMIC EXPLOSIONS

The clinical problems associated with the use of radium and x-rays are now well known, as are the conditions that may arise from the medical use of radioactive isotopes. With the more widespread use of atomic power and fissionable material by industry in the future, more problems concerning clinical medicine and industrial hygiene will arise. Atomic explosions of the future may be of civilian origin, such as an industrial accident, or may follow an enemy attack.

The commonest clinical condition caused by atomic explosion is blast injury. There are two main types: the direct, which results from the shock wave of the explosion, and affects mainly the air-containing cavities of the body such as the lungs and gastrointestinal tract and gives rise to massive hemorrhage or perforation; and the indirect, which is associated with flying débris and trauma. It is unnecessary to discuss these clinical entities, which are well known.

Burns are the second clinical condition of importance encountered in atomic explosions. These are of two types. Flash burns are caused by intense radiant heat liberated at the time of the atomic explosion and are found on the exposed portions of the body not covered by clothes. Ordinary burns result from the many fires that may be started. It is unnecessary to elaborate on the care of burns.

The third clinical manifestation is the acute radiation syndrome. It is necessary to consider briefly here the nature and quality of atomic radiations that cause this syndrome:

Alpha particles are nonpenetrating particles that are impeded by the skin and travel only a few inches in air at speeds of about 10,000 miles per second. If ingested or inhaled into the body alpha particles may cause serious tissue damage through ionization effects.

Beta rays can travel about 12 feet in air and can penetrate a thin sheet of glass or metal and are impeded by 2 mm. of brass or by 1 mm. of lead or silver. Because of their increased power of penetration beta rays may cause serious burns and damage to tissue if inhaled or ingested.

Gamma rays have effects similar to those of x-rays. Gamma rays are electromagnetic, are very penetrating and travel at approximately the speed of light — about 186,000 miles per second. Approximately 6 to 8 feet of earth or concrete is necessary to provide protection against this type of radiation.

Neutrons are only present during the time of actual fission of the bomb material. The neutron travels at about a tenth the speed of light and has a range of about 3500 feet. It has great powers of penetration and is not impeded by ordinary concrete buildings. The neutron has the added danger of producing artificial radioactivity in foodstuffs and other materials with which it comes in contact, and the artificially induced radioactive elements in turn emit alpha and beta radiation. In this way almost any substance may be made radioactive.

The site of action of all radiation is the human cell, where an ionization effect is produced. The most sensitive part of the cell is the cell nucleus, but the cytoplasm is also sensitive. Pyknosis and karyorrhexis are phenomena seen in the nucleus after radiation.

The tissues of the body most sensitive to radiation are the white blood cells and the bone marrow. Consequently, after acute massive radiation causing a very low or nonexistent white-cell count, generalized infection supervenes, nonpathogenic organisms normally present in the body becoming invaders. Multiple phagedenic ulcers and infected foci may appear owing to absence of polymorphonuclear leukocytes. It is at this stage in addition to general therapy that penicillin and antibiotics are of great efficacy to tide the patient over this critical period of massive infection. The period of low immunity may persist for several months, with a slow return to normal of the white-cell count. The experience gained at Hiroshima and Nagasaki shows that leukemia developed in a small percentage of patients who recovered.

A second complicating factor of the acute radiation syndrome is hemorrhage associated with thrombocytopenia. Massive hemorrhages may occur into the tissues and gastrointestinal tract. In these conditions, blood and the necessary intravenous therapy are indicated. Associated with thrombocytopenia is generally hepatic damage, with disturbances in the levels of fibrinogen, prothrombin and heparin, and accordingly it may be necessary to include fibrinogen in the general therapeutic measures. As a result of damage to the mucosa of the intestine by radiation, there will be very little absorption from the gastrointestinal tract, with or without nausea, vomiting and diarrhea. Therefore, therapy should be administered parenterally to persons exposed to intense radiation.

In the event of any large-scale disaster such as would result from an atomic explosion or radioactive "fall out" the therapeutic principles outlined above will help physicians establish medical treatment for the large number of casualties that may be encountered.

THOMAS F. MAHER, M.D., D.P.H.
Executive Medical Officer

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CORRESPONDENCE

REGARDING OSMOTIC PRESSURE IN DIABETES INSIPIDUS

To the Editor: I have a few comments to make about the paper by Dreifus, Frank and Bellet, "Determination of Osmotic Pressure in Diabetes Insipidus: A new diagnostic test," which appeared in the December 30 issue of the *Journal*.

Although this might be listed as a new diagnostic test for diabetes insipidus, in my opinion, from a diagnostic point of view, the authors are proposing a complicated and cumbersome set of determinations to obtain information that can be derived much more simply — that is, demonstration of the well documented and well known fact that patients with diabetes insipidus cannot make a concentrated urine and, indeed, cannot approach a urinary concentration equivalent to that of plasma. However, I cannot see why measuring osmotic pressure of urine and plasma gives one any more information than simply determining specific gravity of the urine under the circumstances that the authors describe. It is true that there is not complete correlation between osmotic pressure of the urine and the specific gravity, but this is so close that for clinical testing the urinometer does as well as measurement of the freezing point to obtain total osmotic pressure. Thus, although their data are correct, for diagnostic purposes I do not see what the test has to add. I should also question their statement that a patient with psychogenic polydipsia and polyuria will always have a greater solute concentration of urine than blood after water has been withheld for three hours and fifteen minutes. Whether they would or not would depend on the water load that the patient had ingested before the withdrawal of water. If this has been high, osmotic pressure might still be below that of plasma. The authors present no data on this point.

Charles H. Burnett, M.D.

Chapel Hill, North Carolina

NOTICES

ANNOUNCEMENTS

Dr. Louis H. Nason announces the removal of his office from 474 Beacon Street to 416 Marlborough Street, Boston.

Dr. Maurice S. Rothman announces the removal of his offices to 1200 Hancock Street and 47 Russell Park, Quincy Center, for the practice of internal medicine and cardiology.

Dr. Melvin I. Shoul announces the removal of his office from 474 Beacon Street to 416 Marlborough Street, Boston.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The annual meeting of the New England Society of Anesthesiologists will be held in Bigelow Amphitheater, Massachusetts General Hospital (afternoon session), and the library of the Harvard Club (evening session) on April 1, starting at 2:30 p.m., with Dr. Henry K. Beecher as chairman. The program is as follows:

2:30 - 2:50 p.m. Cardiac Arrest at the Massachusetts General Hospital, 1924-1954. Dr. Bernard D. Briggs.

3:00 - 3:20 p.m. Physiologic Interrelation between the Thyroid and the Adrenal Medulla during Anesthesia. Dr. William R. Brewster, Jr.

3:30 - 3:50 p.m. Reaction to Sensation as the Effective Site for Drug Action. Dr. Henry K. Beecher.

4:00 - 4:20 p.m. Citric Acid Intoxication during Massive Blood Transfusions. Dr. John P. Bunker.

5:00 - 7:30 p.m. Refreshment and dinner.

7:30 - 8:00 p.m. Business meeting.

8:00 - 9:00 p.m. The Diagnosis and Treatment of Difficult Pain Problems. Dr. James C. White.

MICROCIRCULATORY CONFERENCE

The second microcirculatory conference for physiology and pathology, sponsored this year by the American Association of Anatomists, will be held at the Benjamin Franklin Hotel, Philadelphia, on April 5.

The topic of the meeting will be "Vascular Patterns as Related to Function." The meeting will be open to interested persons.

HYMAN MORRISON LECTURE

The Hyman Morrison Lecture of the Phi Lambda Kappa Fraternity will be delivered by Dr. John Enders, who will speak on the topic "Measles and Viruses from an Unknown Epidemic Exanthem," in the auditorium, Beth Israel Hospital, Boston, on February 25 at 8:30 p.m. All interested persons are invited.

HARTFORD MEDICAL SOCIETY

The program for February 21 through April 18 is as follows:

February 21. Chronic Pulmonary Insufficiency. Dr. Richard L. Riley.

March 7. Routine Orders and Humbug. Dr. Samuel P. Harbison.

March 21. Gastrointestinal Bleeding. Dr. Thomas A. Warthin.

April 4. Bright's Disease in Children. Dr. Conrad M. Riley.

April 18. Medical Aspects of Mitral Commissurotomy. Dr. Louis A. Soloff.

The above lectures will be held in the Hunt Memorial Building, Hartford, at 8:30 p.m.

STATE UNIVERSITY COLLEGE OF MEDICINE AT NEW YORK CITY

The annual alumni day of the State University College of Medicine at New York City will be celebrated on April 30. The scientific session will be held in Polhemus Clinical Hall in the morning. The dinner dance in the evening will be for the benefit of the Research, Scholarship and Student Loan Fund and will be held at the Hotel Granada, 268 Ashland Place, Brooklyn.

AMERICAN PSYCHIATRIC ASSOCIATION (MASSACHUSETTS DISTRICT BRANCH)

The Massachusetts District Branch of the American Psychiatric Association announces two meetings, to be held in the Boston Medical Library at 8:15 p.m., on the following dates:

February 25. Narcissism, the Body Image and the Body Scheme. Dr. W. Clifford M. Scott, McGill University Faculty of Medicine.

April 1. Dr. Robert G. Heath, Tulane University of Louisiana School of Medicine.

INTERNATIONAL COLLEGE OF SURGEONS

The Woman's Auxiliary of the United States and Canadian sections of the International College of Surgeons invites two residents or fellows in training in surgery to attend the annual meeting of the College to present a suitably prepared clinical or scientific paper. The College will provide transportation and living expenses (not exceeding $300) for the time of the meeting; compensation will be based on the distance traveled. The meeting will be held in Philadelphia, Pennsylvania, September 12-15. Further information may be obtained from the Scholarship Committee, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10, Illinois.

INTERNATIONAL COLLEGE OF SURGEONS SCHOLARSHIP

The Woman's Auxiliary of the United States and Canadian sections of the International College of Surgeons announces a scholarship of $3000 available to a young American or Canadian surgeon who wishes to study abroad. The sum will cover transportation and living expenses. The recipient is expected to spend at least ten months of the year as a resident or fellow in a teaching center in one of the countries of Europe or South America. Further information may be obtained from the Scholarship Committee, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10, Illinois.

PHI DELTA EPSILON FRATERNITY LEON LEVINSON FUND

The Graduate Club of Boston of the Phi Delta Epsilon Fraternity announces the formation of a fund to be established at Tufts College Medical School in memory of the late Dr. Leon Levinson. Interested persons may obtain details from Dr. Edward L. Zarsky, 422 Beacon Street, Boston.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY–APRIL. Postgraduate Medical Institute. Page 451, issue of September 9.

FEBRUARY–MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

FEBRUARY 17–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

FEBRUARY 21–APRIL 18. Hartford Medical Society. Page 289.

FEBRUARY 21–MAY 9. Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

FEBRUARY 24 and 28. Consultation Clinics for Crippled Children in Massachusetts. Page 155, issue of January 27.

FEBRUARY 25, MARCH 11 and 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

FEBRUARY 25. Phi Lambda Kappa Fraternity. Hyman Morrison Lecture. Page 289.

FEBRUARY 25 and APRIL 1. American Psychiatric Association (Massachusetts District Branch). Page 289.

FEBRUARY 26 and 27. Mid-Winter Radiologic Conference. Page 1076, issue of December 23.

FEBRUARY 28–MARCH 1. International College of Surgeons, Southwestern Division Regional Meeting. Page 157, issue of January 27.

FEBRUARY 28–MARCH 2. American Orthopsychiatric Association. Page 994, issue of December 9.

MARCH 2. Pharmacology Seminar. Page 246, issue of February 10.

MARCH 5. Massachusetts Academy of General Practice. Spring Clinical Assembly, Worcester.

MARCH 5–MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MARCH 20–23. Aero Medical Association. Page 157, issue of January 27.

MARCH 23–26. International Academy of Proctology. Page 876, issue of November 18.

APRIL 1. New England Society of Anesthesiologists. Page 289.

APRIL 5. Microcirculatory Conference. Page 289.

APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

APRIL 13. New England Surgical Society. Spring Meeting. Boston.

APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

APRIL 30. State University College of Medicine at New York City. Page 289.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

MAY 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 24

THURSDAY, FEBRUARY 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. Presentation of Unusual Thoracic Problems and Surgical Interests. Drs. Dwight Harken and Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Studies on the Pharmacology of Antiarrhythmic Drugs with Comments on a New Drug — Ambonestyl. Dr. Byron B. Clark. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*7:00 p.m. Treatment of Cirrhosis of the Liver. Dr. Elaine P. Ralli. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

FRIDAY, FEBRUARY 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
8:15 p.m. American Psychiatric Association. Massachusetts District Branch. Boston Medical Library.
*8:30 p.m. Phi Lambda Kappa Fraternity. Hyman Morrison Lecture. Auditorium, Beth Israel Hospital.

SATURDAY, FEBRUARY 26

*8:00 a.m. Gynecological Grand Rounds. 6th-floor conference room Carney Hospital, 2100 Dorchester Avenue, Dorchester.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, FEBRUARY 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Medical-Pathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

(Concluded on page xxxiii)

Important!

Folic Acid

The importance of Folic Acid not only in red blood cell formation but in over-all nutrition is now established. When you prescribe a vitamin regimen, particularly for an infant or for a mother-to-be, select a product that contains Folic Acid. Most leading pharmaceutical manufacturers include this member of the vitamin B complex in their multivitamin preparations. This message is presented on their behalf.

Cyanamid Fine Chemicals

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GRAY PHARMACEUTICAL CO., INC.

Products of Research for Medicine

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l-Glutavite

A cerebral tonic for the geriatric patient

Dear Doctor:

A new concept in the treatment of cerebral decompensation in the elderly was recently presented at the New England Postgraduate Assembly. By the use of the unique metabolic stimulant, l-Glutavite, you can demonstrate in your own practice that a majority of typical geriatric complaints can be alleviated. Among many recent clinical observations, certain are especially pertinent:

1. After glutamate therapy, "17 out of the 27 patients were improved.... Of the 17 who improved, 16 improved in action...patients...on occupational therapy do their jobs better...showed more interest in their work." (Himwich, H.E., et al.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.)

2. "Niacin produces often striking therapeutic effects in...'total cerebral decompensation'....A trial with nicotinic acid...is always indicated, particularly in elderly patients." (Lehmann, H.: Proceedings, 27th Annual Conference, Milbank Memorial Fund, New York, Paul Hoeber, Inc., 1952, p. 587.)

Besides these clinical trials, these facts emerge from basic studies:

1. Glutamic acid participates specifically in the nutrition of cerebral tissue.
2. Orally, monosodium levo-glutamate raises blood levels of glutamic acid much more effectively than the free acid itself.
3. Niacin has notable vasodilator effects on cerebral circulation.
4. Thiamine, riboflavin, ascorbic acid and their associated minerals are important in cerebral cellular oxidations.

l-Glutavite* is indicated in the following geriatric states: weakness and fatigue, anorexia, vertigo, insomnia, depression, anxiety, and apathy. l-Glutavite is palatable and taken in vegetable or tomato juice, or sprinkled on prepared foods, stimulates the appetite. 3 to 5 packets daily constitute adequate dosage. We urge you to put this new biochemotherapeutic concept to a practical trial.

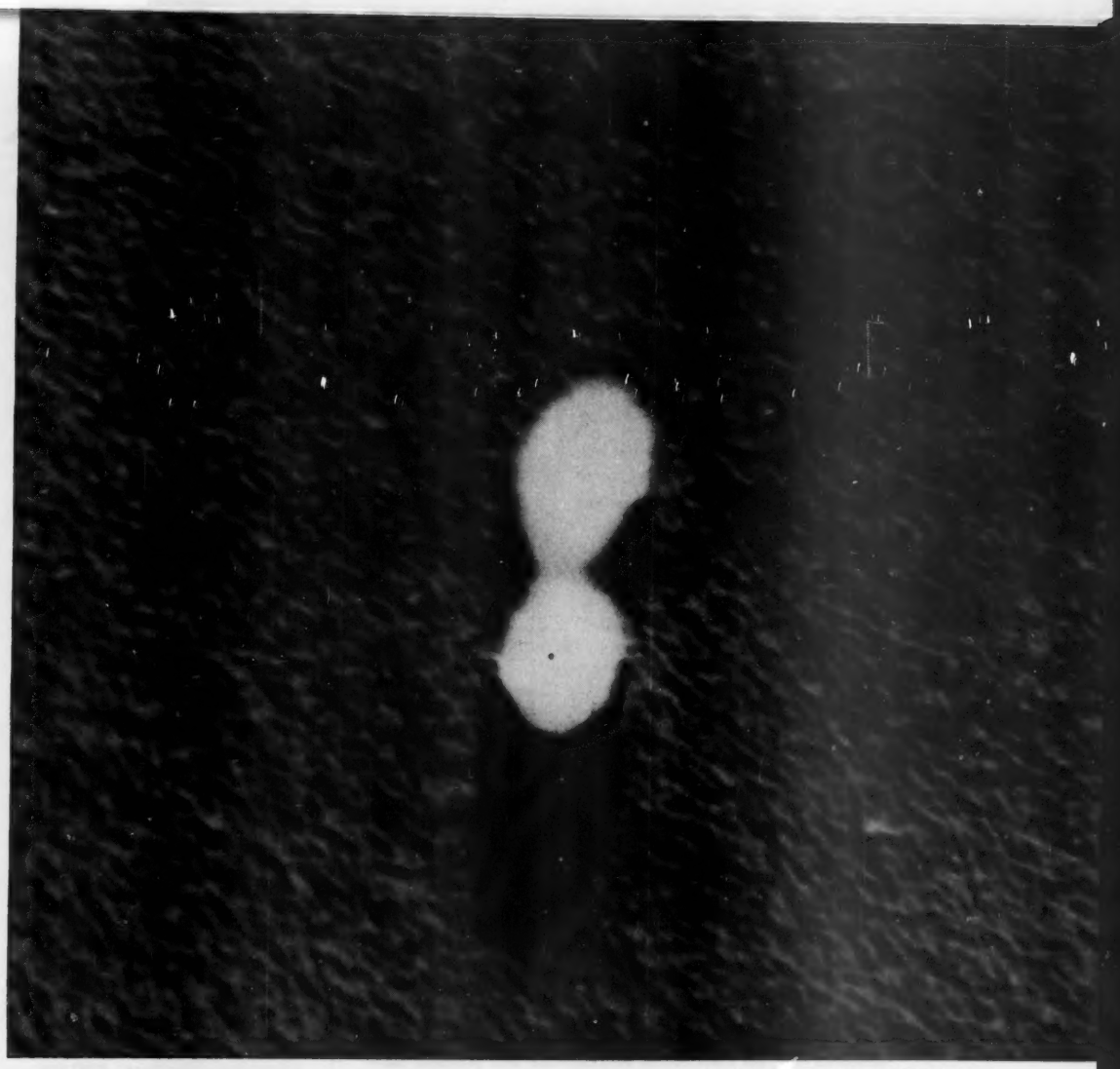
Sincerely,

Francis L. Colpoys M.D.

Medical Director

*Formula (per packet)

Monosodium levo-glutamate	3.48 Gm.
Niacin	45.0 mg.
Thiamine Mononitrate	0.6 mg.
Riboflavin	0.8 mg.
Ascorbic Acid	30.0 mg.
Ferrous Sulfate	11.0 mg.
Dicalcium Phosphate	910.0 mg.



ELECTRON PHOTOMICROGRAPH

Streptococcus faecalis 40,000 X

Streptococcus faecalis is a Gram-positive organism commonly involved in a variety of pathologic conditions, including urinary tract infections • subacute bacterial endocarditis • peritonitis.

It is another of the more than 30 organisms susceptible to

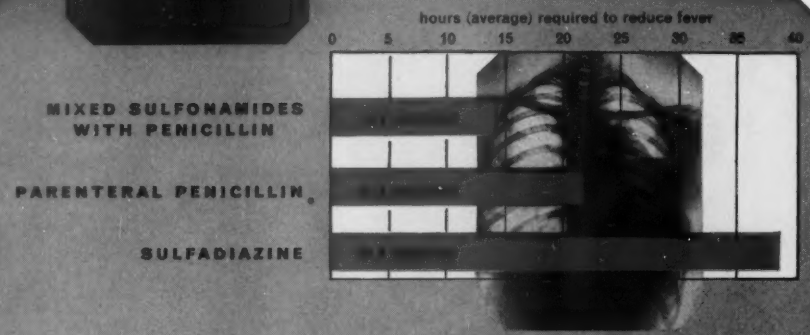
PANMYCIN*

100 mg. and 250 mg. capsules
250 mg./tsp. oral suspension (**PANMYCIN** *Readimixed*)

Upjohn

*TRADEMARK, REG. U. S. PAT. OFF

combined action means faster patient recovery



Vollmer, Pomerance and Brandt observed that the administration of sulfonamide mixtures when combined with penicillin reduced fever in patients with pneumonia more rapidly than sulfadiazine or penicillin alone.*

the preferred quadri-sulfa mixture...

DELTAMIDE® *w*/penicillin

combines 4 of the most useful sulfonamides with penicillin for—

a wider antibacterial spectrum

the advantages of a sulfonamide combination: faster therapeutic blood levels and better sustained; higher solubility in the urine; greatly reduced renal toxicity and lessened side-effects.

the true potentiation of action that occurs with the use of sulfonamide mixtures

the truly synergistic action that occurs when sulfonamides and penicillin are combined

*Vollmer, H.; Pomerance, H. H., and Brandt, I. K.: New York State J. Med. 50: 2293, 1950.

Each tablet or teaspoonful of the pleasant-tasting **chocolate-flavored suspension contains:**

DELTAMIDE	DELTAMIDE *w*/penicillin
0.167 Gm. sulfadiazine	0.167 Gm.
0.167 Gm. sulfamerazine	0.167 Gm.
0.056 Gm. sulfamethazine	0.056 Gm.
0.111 Gm. sulfacetamide	0.111 Gm.
— penicillin G	250,000 Units

Deltamide

Tablets: Bottles of 100 and 1000.

Suspension: Bottles of 4 and 16 oz.

Deltamide *w*/penicillin

Tablets: Bottles of 36 and 100.

Powder for Suspension: 60 cc. bottles to provide 2 oz. of suspension by the addition of 40 cc. of water.

also available **DELTAMIDE**

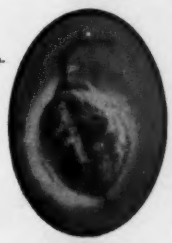
THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

EXPLOSION=

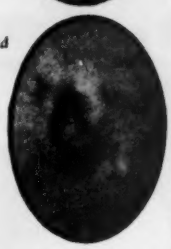
OF TRICHOMONADS WITHIN 15 SECONDS OF CONTACT WITH VAGISEC

A NEW AGENT, Vagisec, reaches deeply buried and surface trichomonads and explodes them within 15 seconds. No other trichomonacide has this effect.

The Davis technic. Vagisec liquid is the trichomonacide developed as "Carlendacide" by Dr. Carl Henry Davis, well-known gynecologist and author, and C. G. Grand, research physiologist. Over 100 leaders in obstetrics and gynecology tested this new agent, using the Davis technic, and reported "better than 80 per cent of cures among non-pregnant patients with one course of treatment."[1]



1. *Microphotograph (phase-contrast microscope) of a trichomonad*



2. *Trichomonad "exploded" within 15 seconds of contact with Vagisec, diluted as douche*

Synergistic action. Vagisec combines a chelating agent to capture the calcium of the calcium proteinate, a wetting agent to remove lipid material and a detergent to denature the protein. Result, the trichomonad swells up and bursts.

Thorough penetration. Vagisec penetrates the cellular debris and mucoid material lining the vaginal wall and buried between the rugae. It reaches trichomonads, hidden and surface.

Course of treatment. Dr. Davis recommends office treatment and home treatment and the use of both Vagisec liquid and jelly. "For a small percentage of women who have an involvement of cervical, vestibular or urethral glands, other treatment will be required."[1]

Office treatment. Expose vagina with speculum. Wipe walls dry with cotton sponges and wash thoroughly for about three minutes with a 1:250 dilution of Vagisec. Dry with cotton sponges. There is no tampon or messy discharge or staining. Six office treatments are recommended.

Home treatment. Prescribe both Vagisec liquid and Vagisec jelly for home treatment. Patient inserts Vagisec jelly each night and douches with Vagisec (1 teaspoonful to a quart of warm water) each morning except on office treatment days. Treatment continues through two menstrual periods. Four weeks after the course, the douche is omitted at least three days and the patient re-examined. Continued douching with Vagisec two or three times a week helps to prevent re-infection.

Summary. The Davis technic (Vagisec) reaches deeply buried trichomonads and explodes them in 15 seconds. It is a triple attack—office treatment, home treatment with jelly at night, and home treatment with liquid in the morning. Vagisec has been clinically tested and proved fast and effective. It is non-toxic.

1. Davis, C. H.: J.A.M.A., 157:126 (Jan. 8) 1955.

JULIUS SCHMID, INC. *Gynecological Division*

423 West 55th Street, New York 19, N. Y.

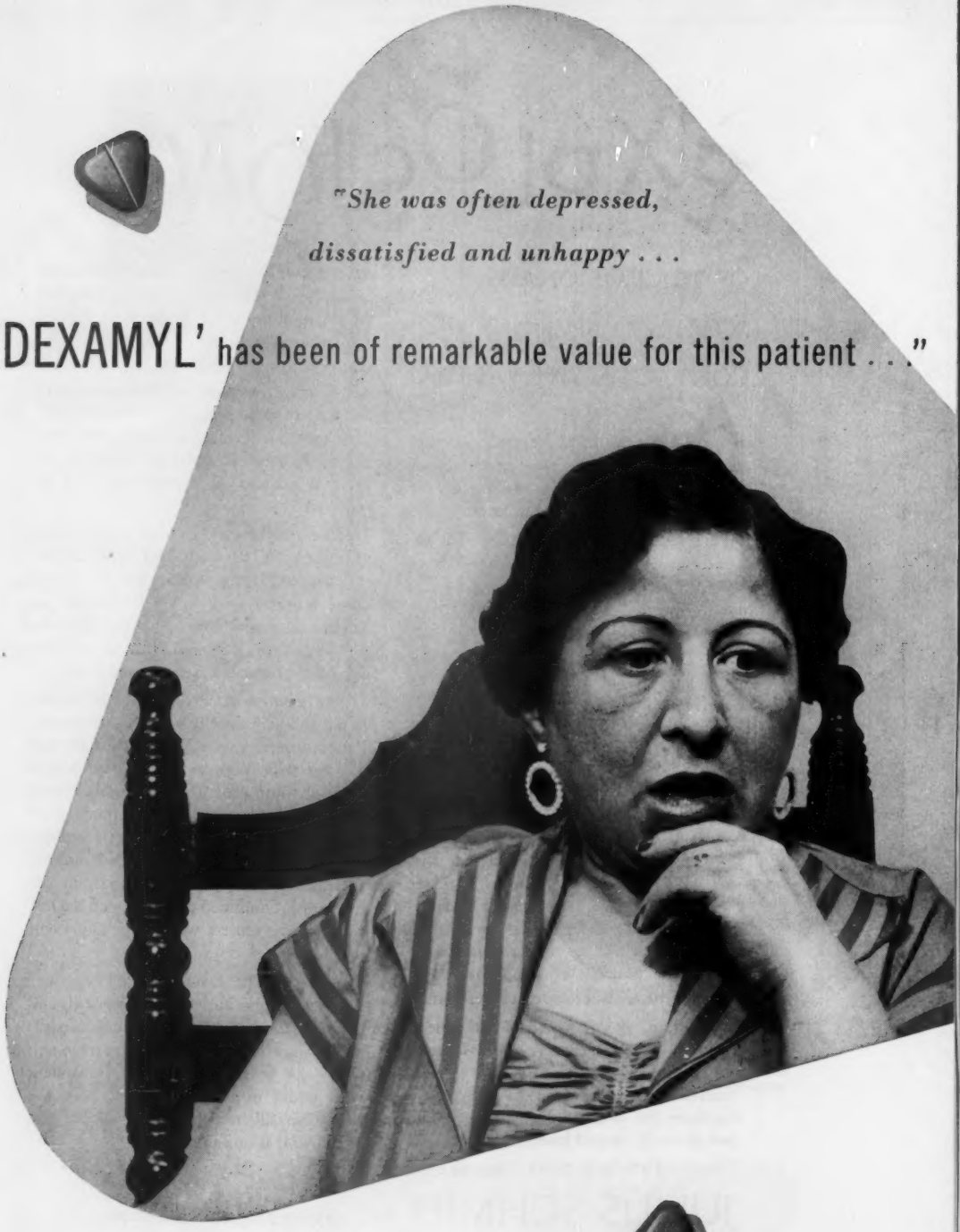
VAGISEC IS THE TRADE-MARK OF JULIUS SCHMID, INC., FOR PRODUCTS TO BE USED IN THE CONTROL OF VAGINAL TRICHOMONIASIS.

Active ingredients: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, Vagisec jelly contains Boric acid, Alcohol 5% by weight.

"She was often depressed,

dissatisfied and unhappy . . .

'DEXAMYL' has been of remarkable value for this patient . . ."



patient: "She was often depressed, dissatisfied and unhappy . . .
"Menstrual irregularities, osteoarthritic pains, climacteric disorders, plus the general cares of married life have brought about a variety of complaints."

medical treatment: 'Dexamyl', 1 tablet, t.i.d.

response: "'Dexamyl' has been of remarkable value for this patient . . . it reduces the tension . . . relieves her insidious uneasiness."

(This unposed photograph was taken during the patient's interview with her physician, a general practitioner. The case report is in his words.)

To help restore tranquility, optimism and a feeling of well-being to the patient who is ANXIOUS and DEPRESSED:

DEXAMYL*

tablets—elixir—Spansule† capsules

Each 'Dexamyl' Tablet or teaspoonful (5 cc.) of the Elixir contains:

Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.)	5 mg.
Amobarbital	½ gr.

also available: 'Dexamyl' *Spansule* (No. 1), containing the equivalent of *two* Tablets; 'Dexamyl' *Spansule* (No. 2), containing the equivalent of *three* Tablets.

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†T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of sustained release capsules

broad spectrum antibiotic of choice

STECLIN

SQUIBB TETRACYCLINE

promptly reaches high levels in the urine

crosses the intact meningeal barrier more readily than the other broad spectrum antibiotics

produces higher blood levels than the other broad spectrum antibiotics

less gastrointestinal side effects than the other broad spectrum antibiotics

Minimum adult dose: **250 mg. q.i.d.**
250 mg. capsules, bottles of 16 and 100.
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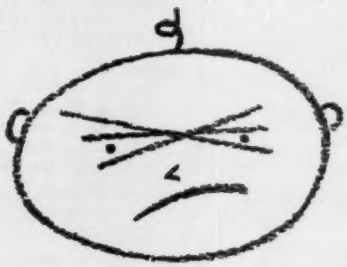

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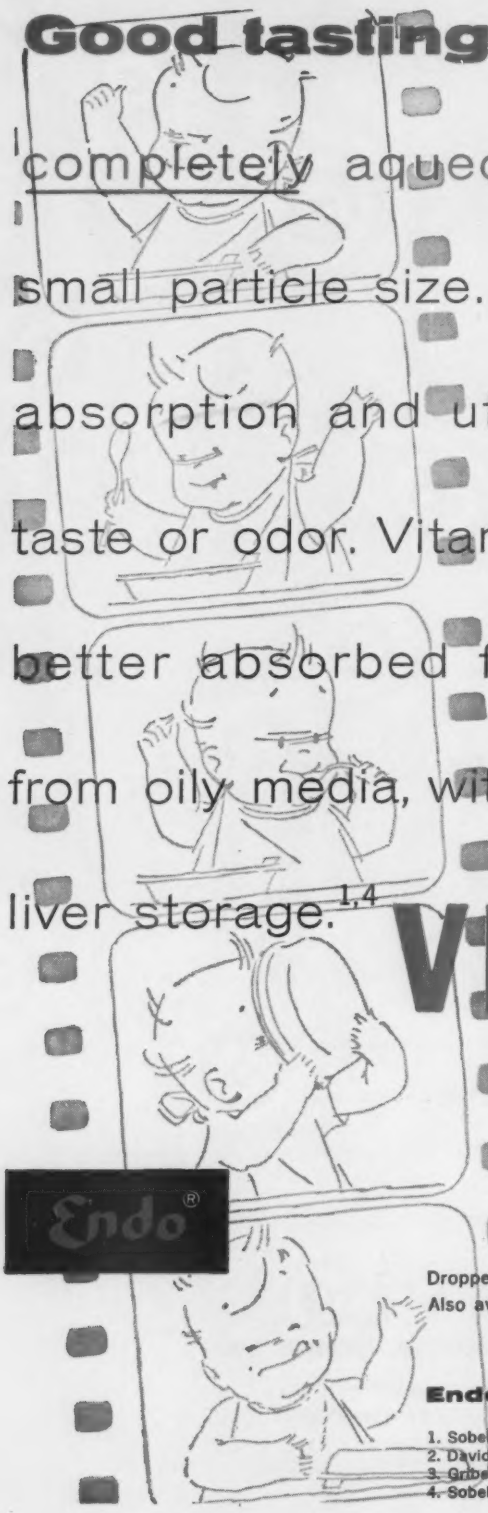

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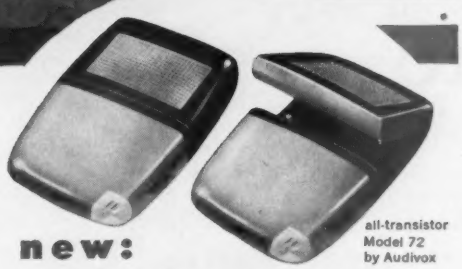

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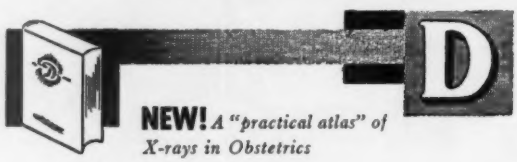

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*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, MARCH 1

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Combined Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Drs. Patterson and MacMahon. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. A Concept of Total Hepatic Lobectomy. Dr. George T. Pack. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, MARCH 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital. Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
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*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
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12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
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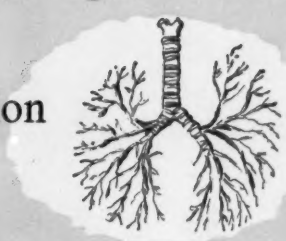

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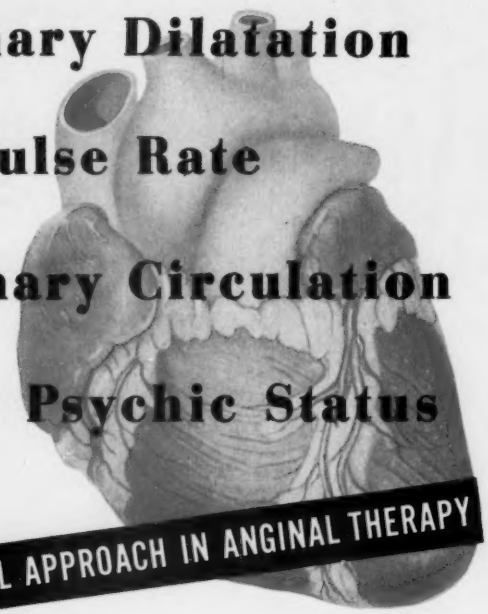

THE NEW, MORE SUCCESSFUL APPROACH IN ANGINAL THERAPY

PENTOXYLON combines the bradycrotic, tranquilizing, stress-relieving effects of Rauwiloid® 1 mg. with the prolonged coronary vasodilating influence of pentaerythritol tetranitrate (PETN) 10 mg.

Reduced heart rate lengthens diastole and leads to better coronary filling and wider stroke volume.

This new approach reduces nitroglycerin need, in many instances obviates it; increases exercise tolerance, reduces anxiety, allays apprehension, and often produces objective improvement demonstrable by electrocardiogram.

Dosage: one to two tablets q.i.d. In bottles of 100 tablets.

PENTOXYLON™

Each tablet contains pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid® 1 mg.

Equally indicated in normotensive and hypertensive patients, since Rauwiloid lowers elevated blood pressure but does not affect normal tension.

Riker LABORATORIES, INC., LOS ANGELES 48, CALIF.